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Burden of Healthcare-Associated Infections in Mainland Portugal: DALYs and Costs

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Abstract

Infection diseases (ID) have existed for a long time provoking many people's death throughout human history. They were recognised as infectious in early epidemics but, due to lack of knowledge, the true epidemiology of disease and the efforts to control them failed. Only in the XV century the fact that these infections were transmitted by air began to be considered and only in the XX century the antibiotics were created. In the XIX century Sammelweiss documented the first healthcare-associated infection (HAI) demonstrating that IDs could be acquired in medical facilities.

This work is about the impact of these infections in Mainland Portugal and the quantification of its burden of disease. It is composed of two studies. The first is based on Cassini et al. [1] and measures the burden of disease of some important HAIs using the disability-adjusted life years (DALY). The second estimates the costs of the same infections in the public hospitals of Mainland Portugal.

In 2016, healthcare-associated urinary tract infection (UTI) was the HAI with the highest number of cases (3679) and DALYs (39,322, representing 33.64% of the total DALYs). It is also the infection with the largest DALY per 100,000 inhabitants (4,448 per 100,000). Surgical site infection (SSI) had the lowest number of DALYs (1,033) and the lowest DALY per 100,000 general population (117 DALYs per 100,000 inhabitants).

The total estimated costs for Portugal were around 33 million of euros. UTI was the most expensive HAI corresponding to 10.93€ million, while healthcare-associated *Clostridium difficile* infection (CDI) was the cheapest corresponding to 0.79€ million. Considering the average cost by admission with HAI, Neo is the one that costs more to the Portuguese healthcare system (SNS, *Sistema Nacional de Saúde*), 4,091.69€.

This work is the first one that uses national data and innovator techniques to estimate the burden and costs of HAI in Portugal. Comparing with other studies in Europe the number of DALYs per admission is higher in Mainland Portugal. Nonetheless, this increased level is aligned with the European Centre for Disease Prevention and Control (ECDC) evidence where Portugal presents one of the highest rates of HAIs in the European Union and European Economic Area (EU/EEA). When comparing the average costs with other countries like France, United Kingdom or United States, the costs of most of these countries are lower, because the prevalence of HAIs in Portugal is higher than in the other countries.

Keywords: Infectious Diseases, Healthcare-associated infection, Disability-adjusted life years, Burden of Disease, Adjusted Cost

Resumo

As doenças infecciosas (DI) existem há muito tempo provocando a morte de muitas pessoas ao longo da história do ser humano. Estas foram reconhecidas como infecciosas nas primeiras epidemias, mas devido à falta de conhecimento da verdadeira epidemiologia da doença, os esforços para as controlar falharam. Apenas no século XV é que o facto de estas infeções serem transmitidas pelo ar foi considerado e apenas no século XX é que os antibióticos foram inventados. No século XIX Sammelweiss documentou a primeira infeção associada aos cuidados de saúde (HAI, *Healthcare-Associated Infection*) mostrando que as DI podiam ser adquiridas em instalações médicas.

As HAI são infeções adquiridas pelos utentes quando internados em hospitais ou em lares, sendo responsáveis por milhares de mortes e de elevados custos para os países [2–4], onde Portugal é um dos países com maior incidência de HAI na UE [5]. São, portanto, um problema para a saúde pública e para os diferentes sistemas de saúde tendo de ser vigiados e controlados.

Para esta finalidade é necessário estudar a carga da doença, ou seja, o estudo do impacto de uma ou várias doenças numa população ou região geográfica usando vários indicadores (mortalidade, deficiências associadas, custos, entre outros). Neste trabalho foram considerados os DALY (*Disability-Adjusted Life Years*) e os custos para medir a carga da doença. Foram, também, consideradas 6 HAI para estudo, por serem as mais comuns, pneumonia (P), infeção primária da corrente sanguínea (BSI), sepsis neonatal (Neo), infeções do trato urinário (UTI), infeção do local cirúrgico (SSI) e infeção por *clostridium difficile* (CDI, bactéria presente na flora intestinal) presentes nos hospitais públicos de Portugal Continental, no ano de 2016.

Este trabalho está dividido em dois artigos: o primeiro working paper, baseado em Cassini et al. [1], submetido ao "The Journal of Hospital Infection", mede a carga da doença de algumas HAI usando os DALY. O segundo working paper, submetido à "Acta Médica Portuguesa", estima os custos das mesmas infeções nos hospitais públicos de Portugal Continental.

Os DALY são o número de anos de vida saudáveis que uma pessoa perde devido a morte prematura ou a sequelas devido a uma ou várias doenças. Dividem-se, portanto, em duas componentes, o número de anos de vida devido a morte prematura (YLL) e os anos perdidos devido a doença (YLD). Sendo que o seu cálculo se traduz por: DALY=YLD+YLL.

Em 2016, a UTI foi a HAI com o maior número de casos, enquanto a CDI é a que teve menos casos, não contando com a Neo, pois esta só afeta recém-nascidos até um 1 ano de idade. A faixa etária dos 80 aos 108 é a que tem maior incidência, excluindo os casos de Neo (40.19% do total) e o número de admissões aumenta ao longo da idade, principalmente a partir dos 50 anos.

Em termos de carga da doença a UTI e a P foram as HAI com maior carga com 39.322 DALY e 31,242 DALY, respetivamente, (representando 33,64% e 26.72% dos DALY totais). A SSI foi a que teve uma carga menor, 1033 DALY, porque a maioria dos SSI não implicarem uma admissão no hospital e apenas as SSI severas terem sido registadas na base de dados em estudo. Estes resultados contrariam Cassini et al. [1], onde este coloca a P como a HAI com maior carga da doença. Em contrapartida, são suportados por Jon Otter [6] que também coloca a UTI no top das HAI com mais DALY no mundo.

A infeção com o maior número de DALY por 100.000 habitantes (4.448 por 100.000) é, também, a UTI. O número de DALY por 100.000 bastante superior em Portugal (13.225 em 100.000) comparando com o Cassini et al [1] para a UE/EEA (501 em 100.000). Isto ocorre por três motivos: primeiro, não é possível obter o número direto de HAI na base de dados de Morbilidade Hospitalar (utilizou-se os pesos das HAI nos resultados do inquérito do ECDC de 2017 para estimar as HAI portuguesas). Segundo, a taxa de infeção em Portugal é mais alta do que na EU. Terceiro, este estudo usa o total da população de

Portugal Continental, enquanto Cassini et al [1] utiliza amostras de hospitais na UE/EEA, onde em alguns países foram contabilizados poucos hospitais.

As BSI foi a HAI com o maior número de DALY por admissão, porque o quociente entre o número de DALY da BSI e o número de admissões não é proporcional ao número de DALY da BSI com o número de habitantes. Ou seja, o número de habitantes é superior ao número de admissões levando a resultados diferentes.

Os custos totais estimados para Portugal foram cerca de 33 milhões de euros, sendo que a faixa etária dos 80 aos 108 anos custa cerca de 12 milhões de euros (36.68%) e os indivíduos com menos do que 18 anos são os mais baratos (7.12%). A UTI foi a HAI mais dispendiosa correspondendo a 10,93 milhões de euros, enquanto a infeção *clostridium difficile* (CDI) foi a menos dispendiosa correspondendo a 0,79 milhões de euros.

Considerando o custo médio por admissão com HAI, a infeção neonatal por sepsis (Neo) foi aquela que mais custou ao Sistema Nacional de Saúde (SNS), 4.091,69€, pois o número de admissões desta HAI é baixo, a sua severidade alta e, consequentemente, consumiu mais recursos. Em contrapartida a BSI foi a HAI mais barata, com um custo médio por admissão de 2151,31€.

Este estudo foi o primeiro que usou dados nacionais e técnicas inovadoras para estimar os DALY e os custos das HAI em Portugal. Comparando com outros estudos na Europa o número de DALY por admissão é maior em Portugal Continental. Não obstante, este número está alinhado com as evidências do Centro Europeu para a Prevenção e Controlo de Doenças (ECDC, *European Centre for Disease Prevention and Control*) onde Portugal apresenta uma das maiores taxas de HAI na União Europeia e na Área Económica Europeia (EU/EEA). Quando comparamos os custos médios com outros países como França, Reino Unido ou EUA, os custos destes países são mais baixos, porque a incidência de HAI em Portugal é maior do que nos outros países.

Este estudo é retrospetivo e exploratório, ou seja, é suportado pela informação respetiva ao ano de 2016 apresentando os primeiros resultados nacionais relativos às seis HAI do ponto de vista dos DALY e dos custos, sendo um ponto de partida para outros estudos/análises.

Relativamente à base de dados utilizada, não estamos a considerar casos clínicos, mas casos administrativos e como tal vai depender dos médicos codificadores de cada hospital, havendo assim casos em que ocorre sobrevalorização ou subvalorização das admissões com registo de infeção.

Estes resultados são alarmantes e mostram que é necessário reunir esforços para reforçar as políticas de saúde nesta área. No entanto, esta análise é conservadora e espera-se que a carga total das HAI seja maior, tanto clínica como economicamente. Não obstante, dá-nos um alerta para os custos excessivos com as HAI tornando necessário que a redução destes seja uma prioridade.

Palavras-chave: Doenças Infecciosas, Infeção Associada aos Cuidados de Saúde, DALY, Carga da Doença, Custo Ajustado

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List of Abbreviations

ACSS- Adminitração Central do Sistema de Saúde

AMR- Antimicrobial Resistance

BCoDE- Burden of Communicable Diseases in Europe

BSI- Healthcare-Associated Primary Bloodstream Infection

CDI- Healthcare-Associated *Clostridium Difficile* Infection

D- Death State

DALY- Disability-Adjusted Life Years

DRG- Diagnostic Related Groups

DW- Disability Weight

ECDC- European Centre for Disease Prevention and Control

Eqv. – Equivalent Patient

EU/EEA- European Union and European Economic Area

GDB- Global Burden of Disease

HAI- Healthcare-Associated Infection

I- Incidence

ID- Infectious Diseases

IHME- Institute of Health Metrics and Evaluation

INE- Instituto Nacional de Estatística

IPC- Infection Prevention and Control

L- Loss Function

LL- Lower Length

LOS- Length of Stay

Neo- Healthcare-Associated Neonatal Sepsis

P- Healthcare-Associated Pneumonia

PC- Post-Colectomy State

PPS- Point Prevalence Study

PROM- Patient-Reported Outcome Measures

R- Recovered State

SSI- Healthcare-Associated Surgical Site Infection

SNS- Sistema Nacional de Saúde

UL- Upper Length

Unc. – Number of Uncomplicated People

UTI- Healthcare-Associated Urinary Tract Infection

WHO- World Health Organization

YLD- Years Lost due to Disability

YLL- Years of Life Lost

Chapter 1: Introduction

Epidemics of infectious diseases (ID) have been documented throughout history. In ancient Greece and Egypt there were descriptions of epidemics of smallpox, leprosy, tuberculosis, meningococcal infections, and diphtheria [7].

The morbidity and mortality of infectious diseases profoundly shaped politics, commerce, and culture. Theories about ID have evolved in different timings according to our understanding of the world, sometimes slowly, sometimes with incredible speed [8].

For example, the bubonic plague and its coinfections, measles and smallpox, were the most devastating of the epidemic diseases. In 166 BC the Roman Empire was ravaged by the Antonine Plague (165-180 BC), which likely killed both co-emperors Lucius Verus (130 – 169 BC) and Marcus Aurelius (121 - 180 BC) along with 5 million others [9,10]. Between 1104 and 1110 nearly 90% of Europeans were killed by plague [11].The plague, also known as the Great Plague or Black Death struck again in 1345 and swept across Europe, then spread to Egypt in 1347 on merchant ships carrying rats and fleas infected with the plague bacillus, *Yersinia pestis* [7]. Until 1351, the Black Death killed 24 million Europeans (3 out of 10) and 40 million deaths worldwide [7,12–14]. These waves of bubonic plague fundamentally affected the development of civilizations as well as imposed a genetic bottleneck on those populations exposed to the viruses [8].

Smallpox, on the other hand, was disseminated during the Arabian expansion, the Crusades, the discovery of the West Indies, and the colonization of the Americas. This disease was brought to the New World by Spanish and Portuguese conquerors and the mortality rates were between 60-90%. Smallpox travelled across the Americas, devastating the previously unexposed American populations [15].

Syphilis is another epidemic ID of great historical importance. Syphilis became epidemic in the 1490s as a highly contagious venereal disease in Spain, Italy, and France. By 1530, the venereal spread of syphilis was widely recognized in Europe [16].

In Western medicine, Hippocrates (460-377 BC) was among the first to record his theories on the occurrence of disease. In his treatise *Airs, Water and Places*, Hippocrates dismissed supernatural explanations of diseases and instead attributed illness to characteristics of the climate, soil, water, way of life, and nutrition surrounding the patient [17–20]. It is Hippocrates who invented the terms *endemic* and *epidemic* disease to differentiate those diseases that are always present in population, endemic, from those that are not always but sometimes occurred in large numbers, epidemic [8].

The fact that IDs were contagious was recognized in early epidemics, but because knowledge of the true epidemiology of diseases was lacking, efforts to control the spread of such diseases were flawed. Plague was recognized to be contagious; however, the control measures focused primarily on quarantine and disposal of the bodies and the possessions of the victims [8].

Fracastoro (1478-1553) in his published book (1546), *De contajione, ontagiosis morbis et curatine* (On Contagion, Contagious Diseases, and their Treatment), proposed the revolutionary theory that infectious diseases were transmitted from person to person by minute invisible particles [12,21]. He formulated the idea that infections were spread from person to person by minute invisible seeds, or *seminaria*, that were self-replicating, and acted on the humours of the body to create disease. [8]. Fracastoro postulated that the environment become polluted with *seminaria* and that epidemics occurred in association with certain atmospheric and astrologic conditions [12,21]. He proposed three modes of transmission of contagious diseases: by direct contact from one person to another, through contact with fomites (a term for contaminated articles still used today), and through the air [8].

Based on the observation that smallpox disease conferred immunity in those who survived, intentional inoculation of healthy people to induce immunity was attempted. This process was known as variolation and was advocated by Thomas Jefferson (1743-1826), Benjamin Franklin (1706-1790) and Cotton Mather (1663-1728). In 1796, Edward Jenner (1749-1823), based on the observation that milkmaids were immune to smallpox, greatly improved the process by substituting cowpox in place of the human pathogen. He performed the first vaccine trial on a child with lesions containing cowpox (vaccinia virus) and later showed that the boy was immune to variolation, or challenge with variola virus [22].

Thomas Sydenham (1624-1689) focused on the individual and their illness rather than on trying to differentiate a specific disease. After Sydenham, the Italian physician Giovanni Morgagni (1682-1771) inaugurated the method of clinicopathologic correlation. This new way of thinking about diseases, requiring careful clinical observation, differentiation, and specific diagnosis, led naturally to the search for specific, as opposed to general, causes of illness [8].

Expanding the concept of careful clinical observation of individuals, epidemiologists in the 1800s observed unusual epidemics and performed controlled studies to exposed persons. Epidemiologic theories about the means of transmission of various infectious diseases often preceded the laboratory and clinical studies of the causative organisms [8].

The epidemiology of bacterial diseases also progressed at this time. Ignatz Semmelweiss (1818-1865) demonstrated with a retrospective record review that an epidemic of puerperal fever, or childbed fever, in 1847 at the Vienna lying hospital was due to transmission of infection on the hands of medical students and physicians who went from the autopsy room to the delivery room without washing their hands. In contrast, the women who were delivered by midwives, who used aseptic techniques (by immersing their hands in aseptic solution prior to contact with the patient), had much lower rates of puerperal sepsis [23] (Figure 1.1).

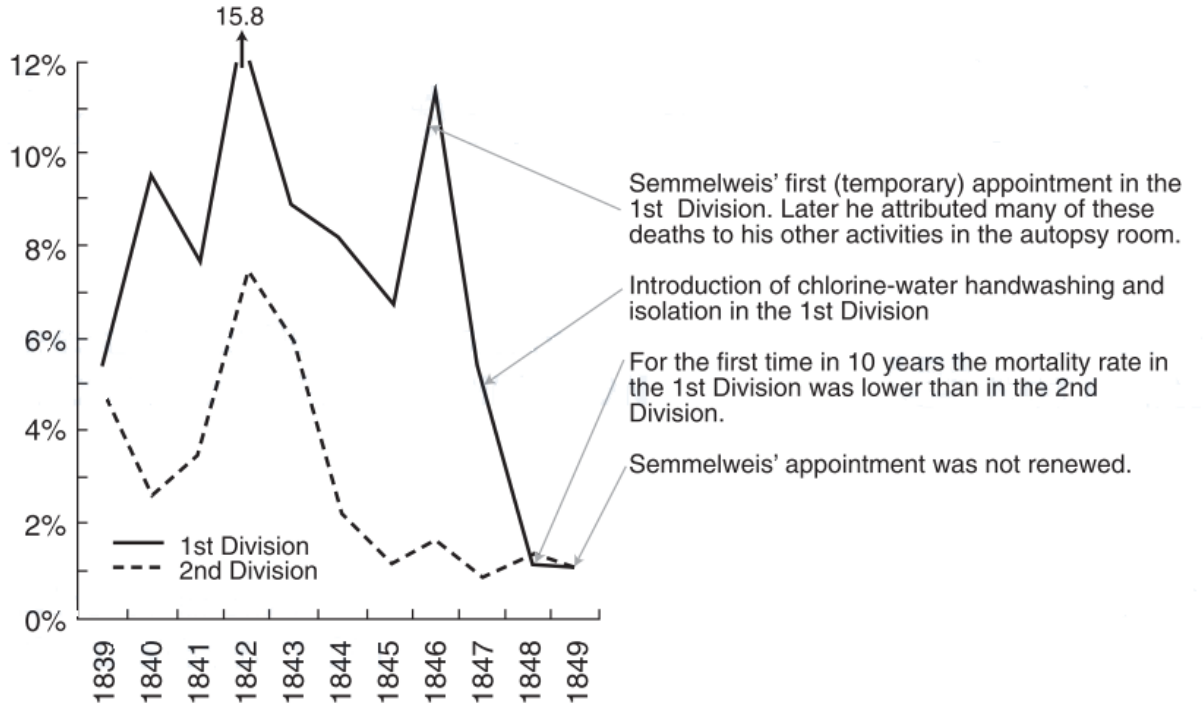


Figure 1.1 - Mortality rates in first and second divisions (wards) of the Department of Obstetrics in the Vienna Lying-In Hospital between 1839 and 1849 [8].

In the area of statistics, Gerolamo Cardana (1501-1576) introduced the concept of probability and described that the probability of any roll of the dice was equal as long as the die was fair [8]. This concept was carried further by Jacques Bernoulli (1654-1705) with the central limit theorem which states that the observed probability approached the theoretical one as the number of observations increased [8]. John Graunt (1620-1674) detailed the number and causes of deaths in London during the preceding third of a century. He used inductive reasoning to interpret the mortality trends and noted the ratio of male to female births and deaths, mortality by season, and mortality in persons living in rural versus urban locations. He examined several causes of deaths over time and constructed the first life table [24]. Chadwick (1800-1890) used health statistics to effectively change public policy. His report "to the Poor Law Commission" (1842) outlined the cost effectiveness of public health. It emphasized the understanding that hygiene was closely related to health, but he also linked mortality to hygiene and health [8].

Anton van Leeuwenhoek (1632-1723) was the first to observe microorganisms describing how materials such as rainwater and human excretions had cocci, bacilli and spirochetes (bacteria) [11]. Louis Pasteur (1822-1895) demonstrated the dependence of fermentation on microorganisms, in 1857, and showed that these organisms came from similar organisms present in the air [25]. And finally, Robert Koch (1843-1910) proposed the "Henle-Koch postulates" to prove that a microorganism was the cause of an infection disease [8].

To study a disease in a controlled setting, some researches resorted to self-experimentations. Angelo Dubini (1813-1902) intentionally exposed his skin to a hookworm inoculum and was unable to find the organism on his exposed skin. After several experiments, he reported the entrance of hookworms into humans by skin penetration of the parasites, rather than by ingestion [8]. Other example is the explosive epidemic nature of yellow fever and malaria when they occurred in Europe and United States. Stubbins Firth (1784-1820) realised a series of self-experiments, and unable to transmit the infection in these experiments concluded that yellow fever was not directly transmitted from person to person [12]. In 1889, Walter Reed (1851-1902) and a yellow fever commission were able to report that the disease was transmitted to humans by the bite of an infected mosquito after several definitive experiments [26]. Later, Reed and his colleagues demonstrated that the causative agent of yellow fever was present in filtered blood leading them to concluded that the causative agent of yellow fever was a virus [26]. This conclusion made yellow fever the first identified viral cause of human disease [8].

In the 1930s and 1940s, Alexander Fleming, Howard Florey and Ernst Chain conducted experiments that led to the demonstration that penicillin, a mould product, was effective against many pathogenic organisms [27]. Penicillin was shown to be effective against syphilis, gonorrhoea and pneumococcal infections [8]. In 1931, Germany scientists at Bayer explored the antibacterial effects of dyes, combining sulphanilamide with a dye produced antibacterial drug (Prontosil). After Florey and Chain published a paper describing a purification technique, penicillin became available in the market (limited) in 1945 [28] with the help of interested drug companies [29]. With the success of penicillin, the race to produce other antibiotics began [29] and the following next years became the "Golden Age" of antibiotic discovery [28].

The success and results of antibiotics were impressive, but at the same time a problem called antibiotic resistance has appeared. This is a problem that surfaced not long after the introduction of penicillin and threatens the usefulness of these important medicines [29].

Almost from the beginning, doctors noted that in some cases, penicillin was not useful against certain strains of *Staphylococcus aureus* (bacteria that causes skin infections). Since then, this problem of resistance has grown worse, involving other bacteria and antibiotics [29].

Since the “Golden Age” of antibiotics, the discovery of new classes of antibiotics has been almost non-existent, as showed in Figure 1.2. It represents a situation that is especially problematic considering the resiliency of bacteria shown over time and the continued misuse and overuse of antibiotics in treatments [30]. Consequently, some serious infectious have become more difficult to treat, forcing doctors to prescribe a second or even third antibiotic when the first treatment does not work [29].

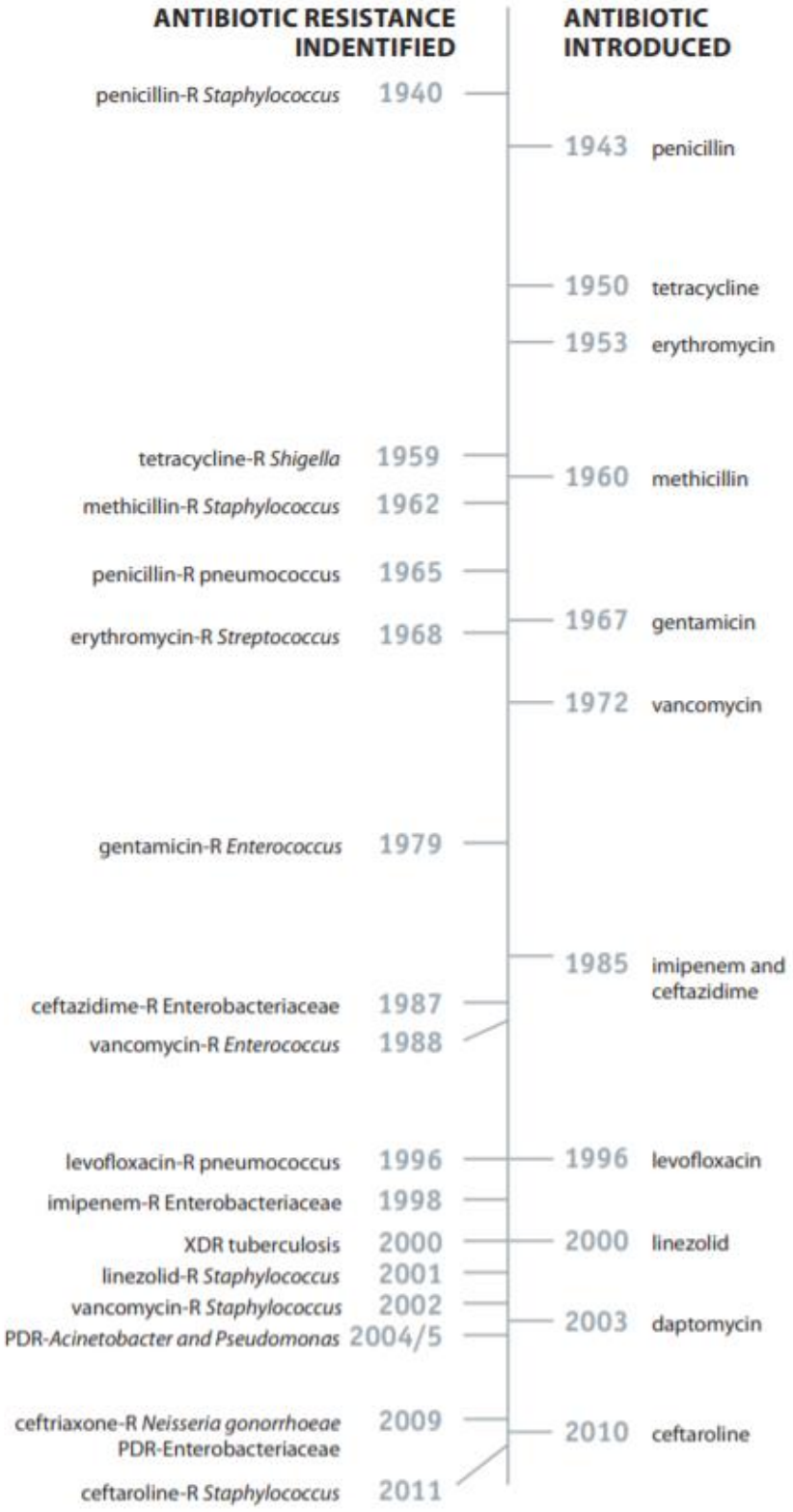


Figure 1.2 - Timeline of antibiotic resistance compared to antibiotic development. [94]

In light of this growing antibiotic resistance, many doctors have become much more careful in the way they prescribe these medicines. In the USA, doctors lowered the numbers of antibiotic prescriptions they prescribed for children with common respiratory infections by about 40% during the 1990s [29].

During the XX century, the average life span of persons in the USA (for example) lengthened by about 30 years, where 25 years of this gain has been attributed to advances in public health. The public health actions to control infectious diseases in the 1900s, included marked improvements in sanitation, water chlorination of nearly all public water supplies, development and use of vaccines to prevent infectious diseases and antibiotics for their treatment, along with improved methods for diagnosis [8] (Figure 1.3).

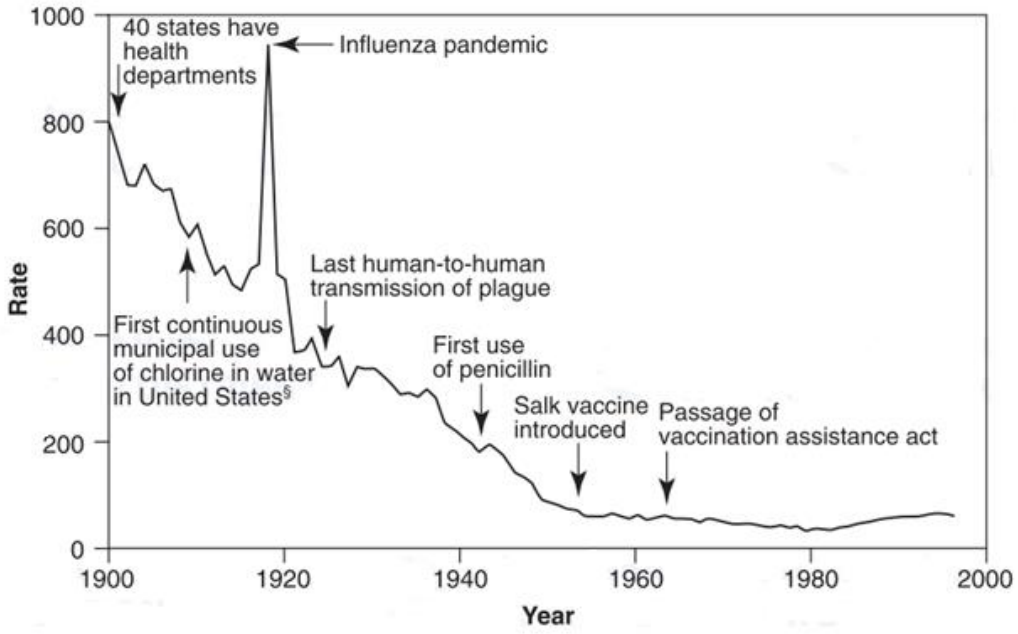
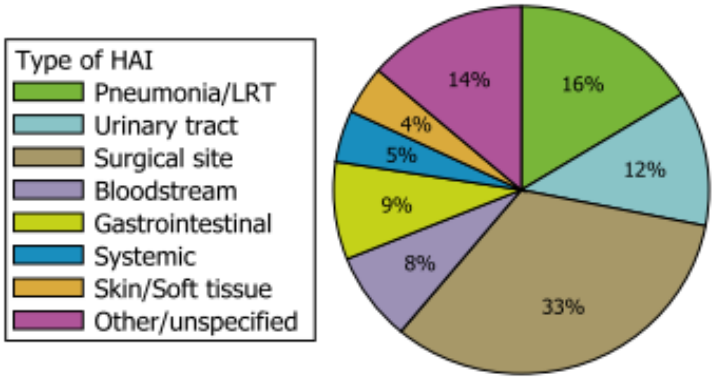


Figure 1.3- Crude death rate due to infectious disease, United States, 1990-1996 [8]

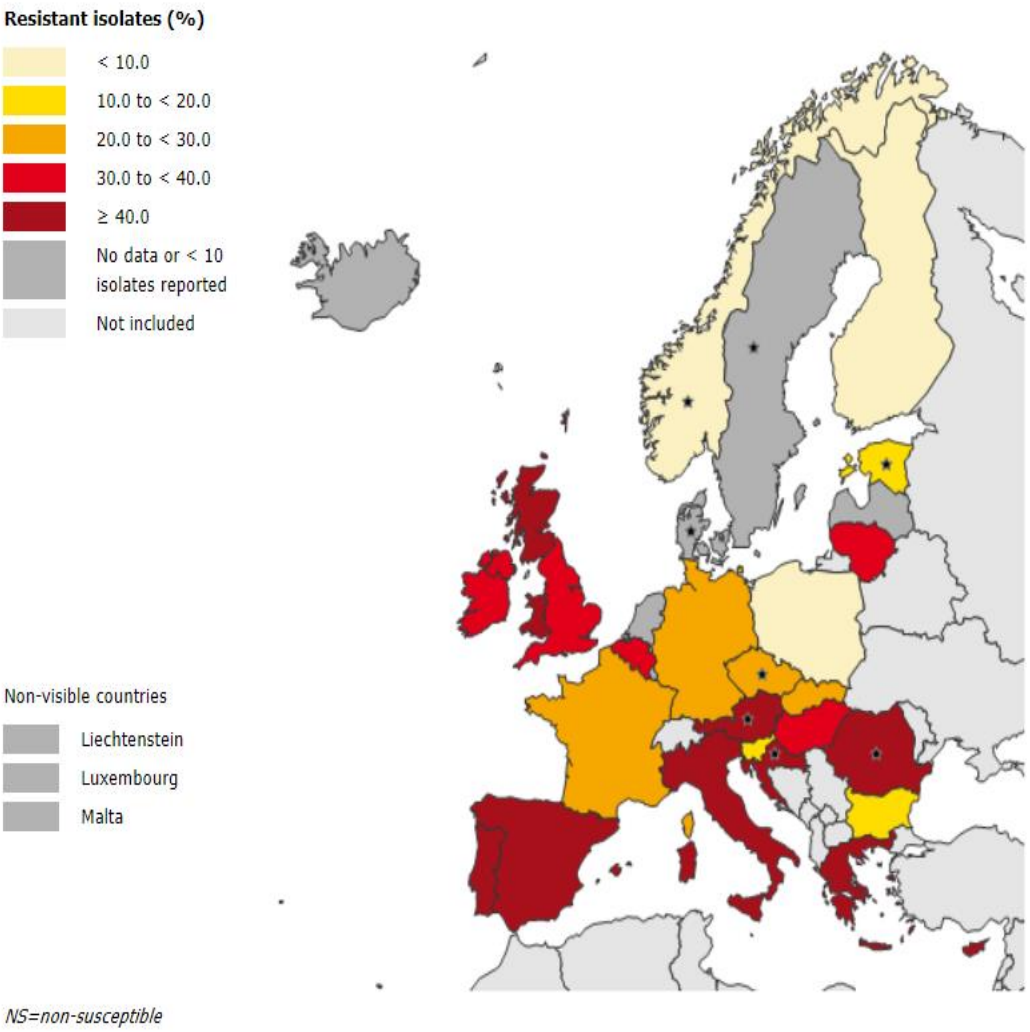
Regarding healthcare-associated infections (HAIs), it was with Ignatz Semmelweiss that the first HAI) was documented demonstrating that IDs could be acquired in medical facilities, i.e., IDs were not acquired only in the community, but also in the facilities where these infections should be healed [31].

HAIs are infections that patients get while receiving treatment for medical or surgical conditions. Each year millions of people acquire a HAI in hospitals of UE and USA (Figures 1.4-1.6), that are responsible for thousands of deaths and costs millions to the states [2–4]. It is evident that this is a problem for public health and for the healthcare systems of the different countries, especially because most of these HAIs are preventable. So, to help in the war against the problem a HAI surveillance must be done.



LRT: Lower respiratory tract

Figure 1.4- Distribution of HAI types by presence of HAI on admission in acute care hospitals, ECDC PPS 2011-2012. [5]



NS=non-susceptible

Figure 1.5 - Percentage of *Staphylococcus aureus* isolates resistant to meticillin (MRSA) in HAIs in acute care hospitals, ECDC PPS 2011-2012. *Country representativeness of the PPS data was optimal or good in 25 (76%) countries, and poor or very poor in 8 (24%) countries. Countries (number of participating hospitals) with poor representativeness were: Austria (n=9), Croatia (n=11), Czech Republic (n=14), Estonia (n=4), Norway (n=7), Romania (n=10) and countries with very poor representativeness were Denmark (n=3) and Sweden (n=4) and are indicated by a "*" in maps and tables [95].

To have an idea of the impact of these infections it is necessary study their "burden of disease". "Burden of disease" is the study of the impact of a disease(s) in a population or a geographical area, using a multitude of indicators: number of infections, deaths, associated deficiencies, years of life lost, quality of life, costs, etc.

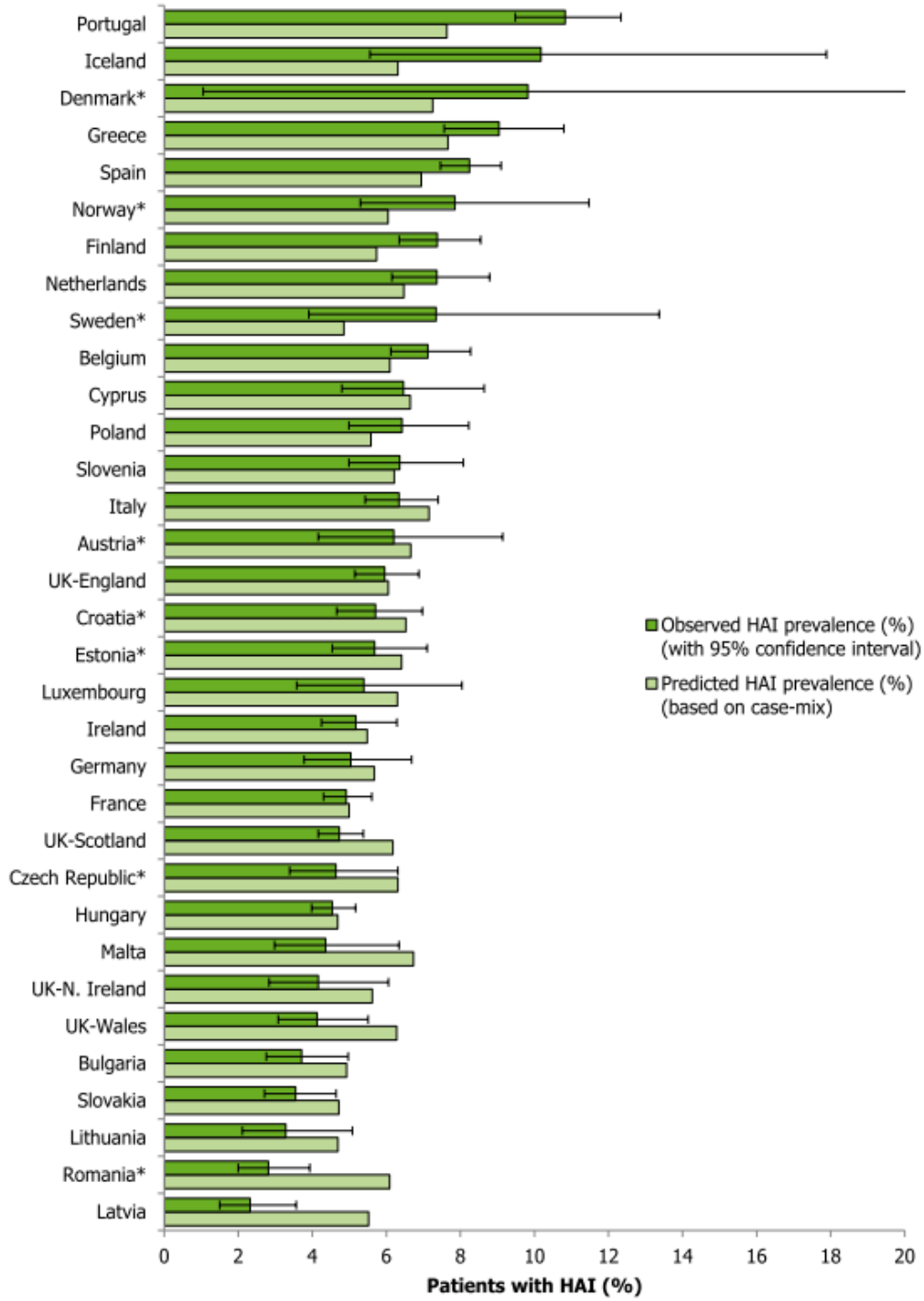


Figure 1.6 - Observed HAI prevalence with 95% confidence intervals and predicted HAI prevalence based on case mix and hospital characteristics, by country, ECDC PPS 2011–2012. *Country representativeness of the PPS data was optimal or good in 25 (76%) countries, and poor or very poor in 8 (24%) countries. Countries (number of participating hospitals) with poor representativeness were: Austria (n=9), Croatia (n=11), Czech Republic (n=14), Estonia (n=4), Norway (n=7), Romania (n=10) and countries with very poor representativeness were Denmark (n=3) and Sweden (n=4). Denmark: upper limit of 95% confidence interval not included HAI prevalence=9.8% (95% CI 1.0– 52.7) [5].

As previously described, Portugal has serious problems with HAIs. How to measure their impact? In Portugal, there are only a few studies of this type [32–34], so a further progress of the quantification of the burden of HAIs in Mainland Portugal is of crucial importance to the citizens, the national healthcare system (SNS, *Sistema Nacional de Saúde*) and the Infection Prevention and Control area (IPC).

In this work the impact of six specific infections were studied and two indicators, disability-adjusted life years (DALYs) and costs, were used to estimate the burden of disease.

The HAIs studied were the six most common, namely: healthcare-associated pneumonia (P), healthcare-associated primary bloodstream infection (BSI), healthcare-associated C. *difficile* infection (CDI), healthcare-associated urinary tract infection (UTI), healthcare-associated surgical side infection (SSI) and healthcare-associated neonatal sepsis (Neo).

DALYs are a health gap measure that combines both time lost due to premature mortality and to non-fatal conditions. They are calculated as the sum of years of life lost (YLLs) due to premature mortality and years lost due to disability (YLDs) [32]. The use of DALYs provides a common metric to aid meaningful comparison of the burden of risk factors, diseases, and injuries [35]. HAI costs will help understand the impact for each admission with HAI, and alert healthcare system responsible of excessive costs.

This is a retrospective and exploratory work, which means that it is supported by the information of the past year of 2016, presenting the first national results about the six HAIs from the point of view of DALYs and costs, as a starting point for further analyses.

The thesis is organized as follows: Chapter 2 presents the study of the impact evaluation of these six infections using the DALY indicator. This work followed Cassini et al, 2016 [1] approach to the burden of disease of the most common six HAIs. This study is presented in a format of a working paper submitted to "The Journal of Hospital Infection", preceded by an introduction. Chapter 3 evaluates the impact of the HAIs costs indicator through a working paper to be submitted to "Acta Médica Portuguesa". It will end with chapter 4 where the results obtained in the previous chapters and some considerations are presented.

Chapter 2: The Burden of Disease of some relevant Healthcare-Associated Infections in Portugal: results of a national exploratory study based on administrative hospital datasets

In this chapter the burden of disease of some relevant infections in Portugal (Mainland) with support of the literature will be discussed. It is based on Cassini et al. [1] article that approaches the burden of disease of six HAIs on the European population, using the DALY methodology. It used the 2011/12 data from the European Centre for Disease Prevention and Control (ECDC) point prevalence survey (PPS) of HAIs and antimicrobial use in European acute care hospitals to estimate the burden of six common HAIs. These HAIs are healthcare-associated pneumonia (P), healthcare-associated primary bloodstream infection (BSI), healthcare-associated C. *difficile* infection (CDI), healthcare-associated urinary tract infection (UTI), healthcare-associated surgical side infection (SSI) and healthcare-associated neonatal sepsis (Neo).

Cassini et al. [1] concluded that the cumulative burden of the six HAI cited above was higher than the total burden of all other 32 communicable diseases included in the Burden of Communicable Diseases in Europe (BCoDE) 2009-2013 study and the model used should allow for the estimation of the potential benefit of preventive measures on the burden of HAIs in the European Union and European Economic Area (EU/EEA).

DALYs are a health gap measure that combines both time lost due to premature mortality and to non-fatal conditions. They are calculated as the sum of years of life lost (YLLs) due to premature mortality and years lost due to disability (YLDs) [30].

For an easier understanding of the working paper, the calculation of the DALY for the CDI will be given as an example.

In order to calculate DALY, the formula is:

$$DALY = YLL + YLD \tag{2.1}$$

with:

$$YLL = \sum_{i=0}^{n} D(i) \times L(i) \tag{2.2}$$

and,

$$YLD = \sum_{i=0}^{n} I(i) \times DW \times Average\ Duration\ of\ Disability \tag{2.3}$$

Where, D(i) is the number of people that died at age i, L(i) is the standard loss function specifying years of life lost for a death age i and I is the incidence at age i (i.e. the number of cases of an infection at age i). DW (disability weight for the condition) and Average Duration of Disability (in years) can be found in the outcome trees of Cassini et al. study [1,36]. The age i varies between 0 and 101 years.

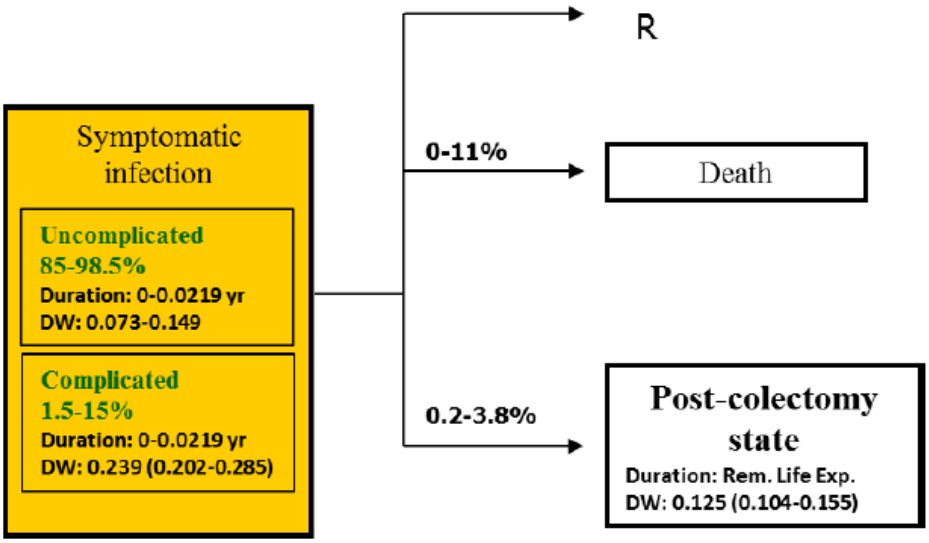


Figure 2.1- Decision tree for CDI [36]

It will be considered that CDI has uncomplicated and complicated cases. The percentage of uncomplicated cases (Unc.) lies between [85-98.5%] and the complicated between [1.5-15%]. So for the uncomplicated cases a percentage of 98.5% was considered, according to Cassini et al. [1], and by complementarity complicated cases had 1.5%. So, starting by the uncomplicated cases we will consider the follow tree (Figure 2.2):

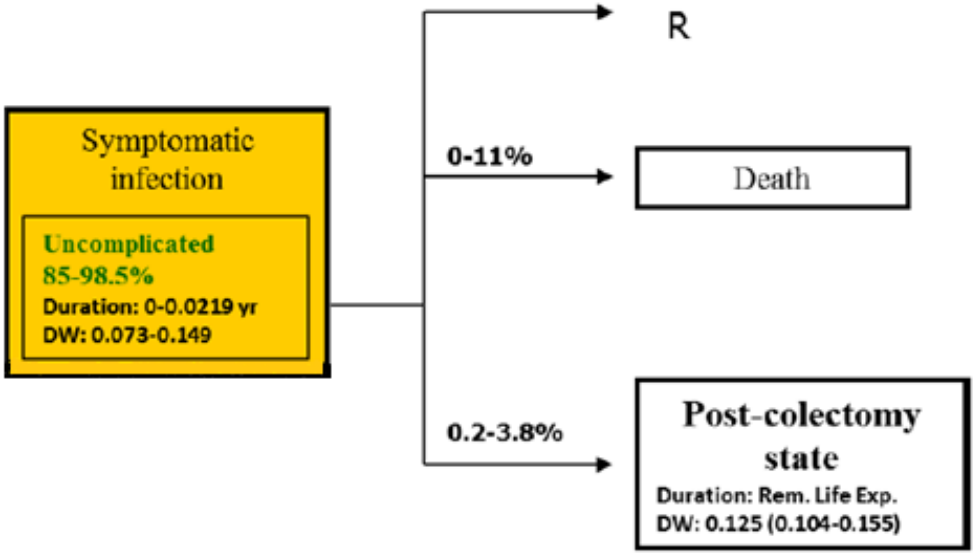


Figure 2.2- Decision tree of uncomplicated CDI [36]

The probability of the other branches will be the same for both cases. It will be considered the highest probability for death (D) and post-colectomy state (PC), P(D|Unc.)= 0.11 and P(PC|Unc.)=0.038, according to Cassini et al. [1]. This means that the P(R|Unc.) = 1-0.11-0.038 = 0.852. Using the incidence at age 0 (Table 2.1) we will have:

$$Unc.(0) = I(0) \times P(Unc.) = 0.474 \times 0.985 = 0.467\ uncomplicated\ people$$

with,

$$Incidence\ (0) = \frac{NC(0)}{\sum_{i=0}^{108} NC(i)} \times 321 = 0.474\ \ people\ with\ CDI \tag{2.4}$$

In (2.4) 321 is the estimated number of cases with CDI in our universe of 11,467 admissions with infection based on the PPS 2017 of ECDC where it was estimated that in 2016, in Portugal, that 43 patients had CDI out of a total of 21,339 patients per day.

Table 2.1- Incidence of CDI by age.

Age	No of cases (NC)	Incidence (I)
0	2	0.474
2	1	0.237
4	3	0.711
5	1	0.237
…	…	…
101	1	0.237
Total	1355	321

Now, to calculate the number of people in the recovered, death and post-colectomy state at age 0:

$$R\ (0) = \ Unc.\ (0) \times\ \mathrm{P(R|Unc.)} = 0.467 \times 0.852\ =\ 0.398\ recovered\ people$$

$$D\ (0) = \ \mathrm{Unc.}\ (0) \times\ \mathrm{P(D|Unc.)} = 0.467 \times 0.11 =\ 0.051\ death\ people$$

$$PC\ (0) = \ \mathrm{Unc.}\ (0) \times\ \mathrm{P}(PC|\mathrm{Unc.}) = 0.467 \times\ 0.038\ \ =\ 0.017\ pos - colectem\ state\ people$$

Secondly, YLL will be calculated, by the formula (2.2) for age 0:

$$YLL\ (0)\ =\ D(0) \times\ L(0) =\ 0.051\ \times 80.78 =\ 4.147\ years\ of\ life\ lost$$

For the calculation of YLD (expression 2.3), recovered people and PC people are the only ones considered. For DW the highest value in the range or the exact value given in Figure 2.2, 0.149 and 0.125 respectively are used. For the Average the highest value in range (0.0219 years) is also used or when it says, "Rem. Life Exp." (remaining life expectancy the standard loss function, L(i) is used. So, for age 0:

$$YLD_R(0) = I(0) \times DW \times Average\ Duration = 0.474 \times 0.149 \times 0.0219 = 0.0015\ years$$

$$YLD_{PC}(0) =\ I(0) \times DW \times Average\ Duration = 0.474 \times 0.125 \times 80.78 = 4.784\ years$$

$$YLD_{Total}(0) = YLD_R(0) +\ YLD_{PC}(0) = 0.0015 + 4.784 = 4.786\ years$$

Now, with YLL and YLD calculated,

$$DALY_{Unc.}(0) = YLD_{Total}(0) + YLL_{Unc.}(0) = 4.786 + 4.147 = 8.933\ years$$

Repeating analogous calculations for each age and summing up at the end the total DALY for the uncomplicated cases is obtained:

$$DALY_{Unc.} = \sum_{i=0}^{n} DALY_{Unc.}(i)$$

For the complicated cases, to calculate $DALY_{Comp.}$, the process is analogue:

$$DALY_{Comp.} = \sum_{i=0}^{n} DALY_{Comp.}(i)$$

Finally, for the CDI DALY, we will have:

$$DALY = DALY_{Unc.} + DALY_{Comp.} = 1529.98\ years$$

2.1 Working Paper I, submitted to "The Journal of Hospital Infection"

The Burden of Disease of some relevant Healthcare-Associated Infections in Portugal: results of a national exploratory study based on administrative hospital datasets

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Summary

Objectives This study aims to estimate the burden of disease of the six most common healthcare-associated infections observed in Mainland Portugal in 2016 using administrative hospital datasets.

Methods The relevant cases for this study were obtained using the National Hospital Morbidity Database, which contains the admissions records for 2016 corrected by data from the European Centre for Disease Prevention and Control (ECDC) Point Prevalence Study. In order to measure the burden of disease the number of disability-adjusted life years (DALY) was chosen as the most appropriate metric. To calculate the DALYs components the weights defined by the literature on outcome trees for six healthcare-associated infections (HAIs) and the standardised life expectancy of National Statistics Institute mortality table 2015-2017 were considered.

Findings In 2016, 11,467 cases of HAIs were estimated. Healthcare-associated urinary tract infection (UTI) and healthcare-associated pneumonia (P) were the infections with the highest number of cases, 32.09% and 24.87%, respectively. The age group [80-108] was the one with the highest rate of HAIs (40.19% of all admissions). The average age of the patients was 68.70 years old with a standard deviation of 34.78 years. The infection with the highest DALY per admission was the healthcare-associated bloodstream infection (BSI) with 13.43 DALYs. UTI had 39,322 DALYs which represents 33.64% of the total DALYs and is also the infection with the largest DALY per 100,000 inhabitants (4,448 per 100,000).

Conclusions This is the first study that uses national data to estimate the burden of HAIs in Portugal. UTI and Pneumonia are the infections with the highest weight in Mainland Portugal and should be the priority in the war against HAIs and its impacts. The surgical site infection (SSI) has the lowest number of DALYs mainly due to the fact that the majority of SSI infections (when they occur) do not imply an admission in the hospital, only severe SSI would have been registered in the database used in the study. The number of DALYs per admission with infection estimated in this work is higher than the DALYs calculated by other studies in Europe. Nonetheless, this increased level is aligned with the ECDC evidence where Portugal has one of the highest rates of HAIs in the European Union and European Economic Area (EU/EEA).

Introduction

The term burden of disease refers to a quantitative estimation of the impact of a disease on a population or geographical region, using a multitude of indicators [37]. Estimation of the burden of disease expressed in disability-adjusted life years (DALYs) is a comprehensive and evidence-based approach to evaluate the burden of a disease that can be used to inform policy making in public health [1]. DALY is a composite measure that accounts not only for the mortality data but also includes short-term and long-term disabilities that result from the disease [1]. DALYs provide a standard metric to aid meaningful comparison of the burden of risk factors, diseases, and injuries [35]. It is also intended to promote an evidence-based approach to assess population health and foster analysis of surveillance data quality and availability. It facilitates the communication of complex health information to decision-makers and provides a tool for the planning and prioritisation of infectious disease prevention, preparedness and control measures [38].

In order to help the promotion of an evidence-based approach to assess population health, the Institute for Health Metrics and Evaluation (IHME) in collaboration with World Health Organization (WHO) develops in a regular basis the Global Burden of Disease Study (GBD) [39]. In its last edition in 2017, by decreasing order, that ischemic heart disease, neonatal disorders, stroke, lower respiratory infections and diarrhoea were the health problems that accounted for more years of life lost (YLL) in the world. Low back pain, headache disorders depressive disorders are the ones who accounted for more years lost due to disability (YLD) worldwide. In Portugal, the estimates pointed out, that stroke, ischemic heart disease, lung cancer and Alzheimer's disease accounted for more YLL, and low back pain, diabetes, headache disorders and depressive disorders accounted for more YLD [40].

In Portugal, there are a few studies using DALYs [32–34], besides the study published in 2018 by the National Directorate of Health [41], which conclude that in 2016, the leading causes of early death (YLLs) were ischemic heart disease, stroke, Alzheimer's disease and lung cancer.

These "top four" health problems are the same that appeared in the year of 2017 [40] only with a different leading order, ischemic heart disease in 2016 and one year later stroke. In 2016, the leading causes of disability (YLDs) were low back and neck pain, sense organ diseases, depressive disorders and migraine, by descending order. Comparing with the data of the IHME website [40] in 2017, low back pain (with more YLDs) and depressive disorders continue on the "top" leading YLDs, along with two new health problems: diabetes and headache disorders.

According to some estimates from the GDB project, IDs (infectious diseases) represent less than 10% of the total burden of disease in Europe [42,43]. There are some difficulties in estimating the burden of IDs for the fact that they occur on very different time scales [44], the relationships with later chronic sequelae are not clearly established [45], infections do not only lead to acute illness but might also result in chronic and long-term sequelae, requiring the use of an incidence- and pathogen- based DALY approach [37,44], and the difficulty to attribute morbidity to a specific pathogen. This incidence and

pathogenic-based approach furthermore allows a proper prediction of potential effects of interventions aiming at preventing infections, which is the primary focus in decision making [37].

Even though the recognition by the scientific community of the importance of the Burden of Disease studies in the Infection Prevention and Control (IPC) area, it is only possible to refer, to our knowledge, two studies that use the DALY metric in IPC: the study of the Burden of Six Healthcare-Associated Infections on European Population Health [1] and the Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015 [46].

The first one [1] refers that a significant proportion of HAIs are preventable, and they are considered to be a marker of patient care quality. In this study DALYs were calculated to estimate the burden of disease of six HAIs and the need for increased efforts for the prevention and control of the HAIs was concluded.

The second one [46] aimed to estimate the burden of five type of infections caused by antibiotic-resistant bacteria of public health concern in countries of the EU and EEA in 2015, qualified by the number of cases, attributable deaths and DALYs. It concluded that the estimated burden of antibiotic-resistant bacteria in EU and EEA was substantial compared to other infectious diseases and provided useful information for public health decision-makers prioritising interventions for infectious diseases.

By giving information through DALYs it will be possible to leapfrog the Portuguese National Health System (SNS, *Sistema Nacional de Saúde*) into another level and promote with an evidence-based approach the infectious disease prevention and control strategies. Furthermore, it can also help improve prioritising and planning public health system [38], like the Slovenian national estimation of the burden of tick-borne encephalitis did with the identification of age groups with the highest DALYs in order to develop more efficient vaccination strategies [47].

Taking into account the gap in Portugal in using DALY for the IPC area, this study aims to characterise the burden of disease of the HAIs in Mainland Portugal and also to compare the results with the ones obtained when the incidence-based DALY methodology using the mindset of Cassini et al. [1] is used.

Methods

To ensure that the previous objectives are achieved, a non-clinical retrospective transversal study was designed, based on HAIs, where increased morbidity, mortality and excess costs are included [1]. The HAIs considered in this study are six, the same considered by Cassini et al in their study [1], i.e.: healthcare-associated urinary tract infection (UTI), healthcare-associated primary bloodstream infection (BSI), healthcare-associated neonatal sepsis (Neo), healthcare-associated C. *difficile* infection (CDI), surgical site infection (SSI), and healthcare-associated pneumonia (P).

For this study, incidence data from the National Hospital Morbidity Database provided by the *Administração Central do Sistema de Saúde*, IP (ACSS) was used regarding the inpatient records of 2016 in Mainland Portugal and the records with, at least, one diagnosis of infection coded by ICD-9-CM were selected. Table 1-A (in the annexs) shows the codes considered per studied infection [48–55].

It is important to refer that if more than one diagnosis was coded for the same type of infection, the infection was counted just one time. On the other hand, if in the same episode, more than one diagnosis was coded for different types of infection it was considered that the patient would have more than one infection.

After the selection of the six infections total cases (159,305 cases with HAIs and non-HAIs; 9.75% of the total records) to achieve the primary goal of the study, i.e., to assess the impact of HAIs, the incidence

of the infections of interest was corrected using the data from the Point Prevalence Study 2017 of ECDC [56], because the data from the National Morbidity Database used in this study contained patients with HAIs and non-HAIs. Then this prevalence was annualised and its percentage was considered according to the total of infections. The number of HAIs was estimated as 11,467 (0.7% of the total).

The number of years of life lost due to premature mortality (YLLs) was calculated compared to a standardized life expectancy [57] (in this case the mortality table of Portugal from 2015-2017, for both genders, was used, provided by INE [58]).

Considering that the DALY (YLL+YLD) is a composite health measure estimating not only the number of years of life lost due to premature mortality (YLL), but also the number of years lived with disabilities (YLD). The number of YLDs in the study population was calculated using the following formula [59]:

$$YLD = I \times DW \times Average\ Duration\ of\ disability \text{ (in years)}$$

In the above expression, I is the incidence of the infection (i.e. the number of admissions with diagnosis of infection in the total number of admissions [60]), DW is the disability weight for the condition used by Cassini et al [1] (i.e., the 'valuation' of time lived in non-fatal health states formalises and quantifies the loss of health for different states of health [59]), corrected with a multiplicative model due to multiple disabilities, specially at elderly age [19] and the Average Duration of the disability (in years) can be found in the outcome trees of Cassini et al. study [36] (the maximum value of the average duration was used for the calculations).

Results

During 2016, there occurred 1,632,375 hospital admission, in Mainland Portugal. To achieve the goals of this study, 159,304 records (9.75%) were selected using the codes of infection previously mentioned which corresponds to patients diagnosed with, at least, one of the infections studied for research.

Considering that the data on the National Morbidity Database cannot distinguish patients with HAIs and non-HAIs, after the previously mentioned correction, the number of cases in the study was 11,467 (0.7% of the total).

The distribution of cases by HAI and by age group is represented in Fig. 2.3, where Urinary Tract Infections (UTI) and Pneumonia (P) are the infections with the more cases, 32.09% and 24.87%, respectively. *Clostridium difficile* infection (CDI) is the one with fewer cases (2.80%), not considering sepsis neonatal (Neo) because it only affects children with less than one year old. The age group of [80-108] is the one that has the highest incidence (not considering Neo) with 40.19% of the total infections.

Analysing the most incident infection per age group, for the [0,17] group, the most incident infection is Neo with a weight of 31.05 %. In the age-groups [18,49] and [50,64] the HAI with more weight is SSI with incidence of 46.58% and 40.30%, respectively. For groups [65,79] and [80,108] years, UTI is the HAI with more cases 31.60% and 39.15%, respectively.

The number of admissions increases with age, especially from [50,64] to [65,79] and then, again, from [65,79] to [80,108]. The number of infections between 18 and 49 years old represents 8.50% of the total admissions in that group age, and the number of infections in the age group of [80,108] only represents 6.48% of the admissions, the lowest percentage.

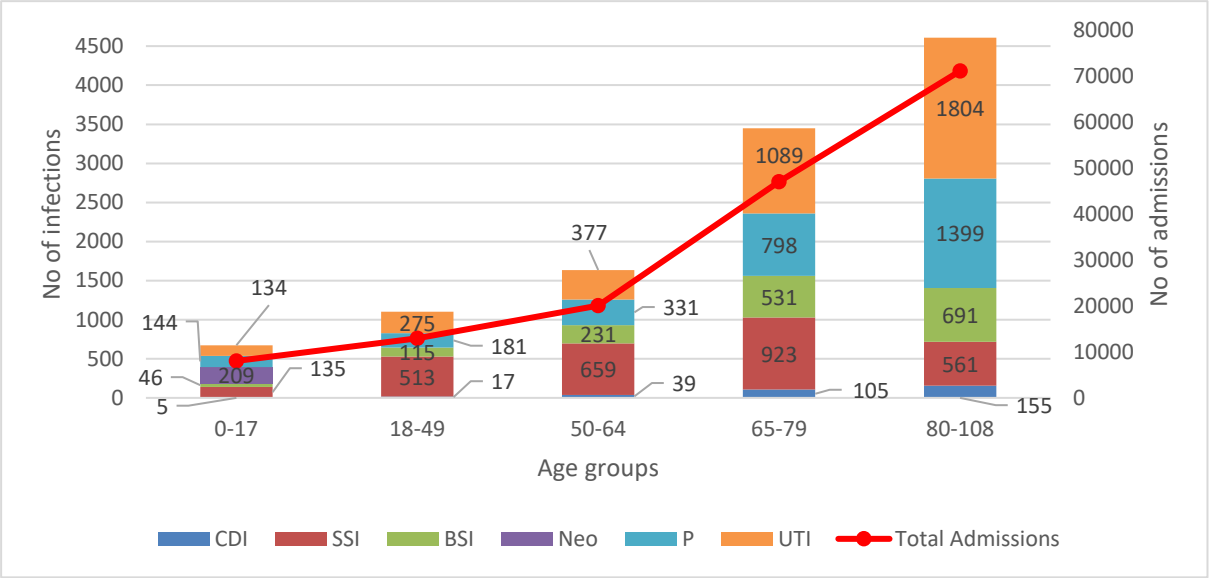

Figure 2.3 - Number of cases by age group of the six healthcare-associated infections (HAIs) considering the total admissions by HAI, Mainland Portugal, 2016

Table 2.2 - The Estimated annual burden of the six healthcare-associated infections, Mainland Portugal, 2016.

Healthcare-Associated Infection	No of HAIs cases estimated for 2016	Average age ± Standard deviation (years)	YLL	YLD	Total of DALYs
Clostridium *difficile* infection (CDI)	321	74.67 ± 34.85	467	1,063	1,530
Surgical Site Infection (SSI)	2,792	61.77 ± 31.73	1,019	14	1,033
Bloodstream infection (BSI)	1,613	72.11 ± 36.38	5,021	16,643	21,664
Neonatal Sepsis (Neo)	209	0.00*	2,364	19,572	22,116
Pneumonia (P)	2,852	72.47 ± 36.5	1,545	29,697	31,242
Urinary Tract Infection (UTI)	3,680	72.92 ± 36.78	2,207	37,115	39,322
Overall	11,467	68.7 ± 34.78	12,623	104,284	116,907

*Null standard deviation (patients are 0 years old).

The estimated burden of the six selected type of HAIs is presented in Table 2.2. UTI is the HAI with higher incidence (33.64%). The average age in this infection is 72.92 years. CDI has an average age of 74.67 years (the highest average age) while SSI has an average age of 61.77 years (the lowest average age).

According to the data, HAIs accounted for 116,907 DALYs in Mainland Portugal in 2016 (YLLs accounted for 10.80% and YLDs for 89.20% of the total).

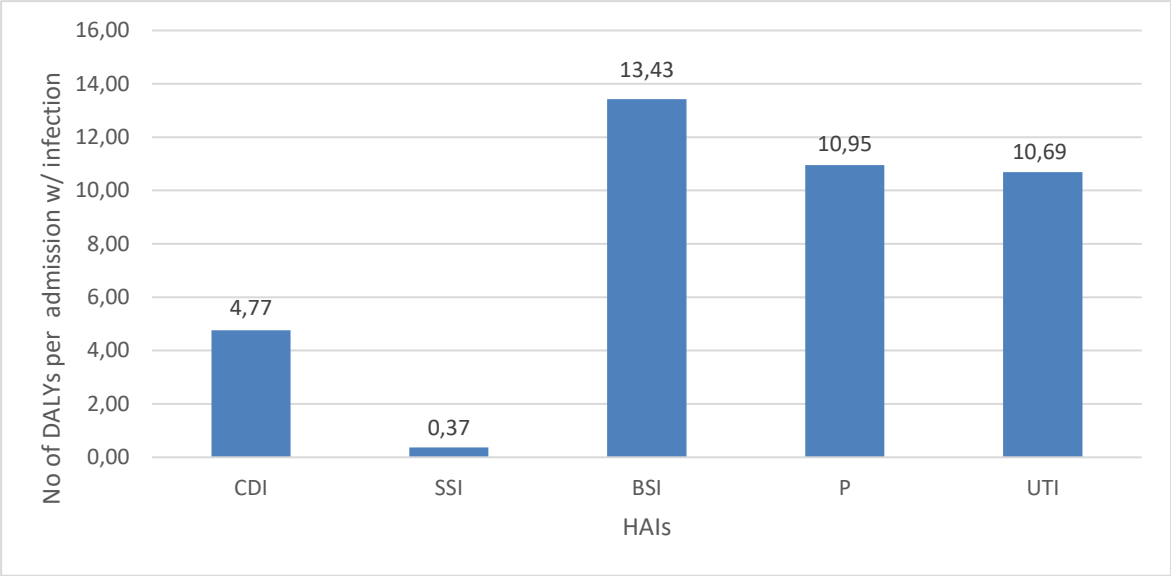

Figure 2.4- Number of DALYs per admission with, at least, one of the six healthcare-associated infections (HAIs), Mainland Portugal, 2016.

When comparing the HAIs by the number of DALYs per admission with infection a total of 40.21 DALYs per admission in the public hospitals of Mainland Portugal (Fig. 2.4) was estimated. It is possible to mention that the HAI with more DALYs per admission is the BSI (13.43 DALYs; 33.41%) and SSI is the hospital-acquired infection with fewer DALYs per admission (0.37 DALYs; 0.88%), Neo is not presented in the figure, but each admission with Neo infection accounts for more than 80 DALYs per case.

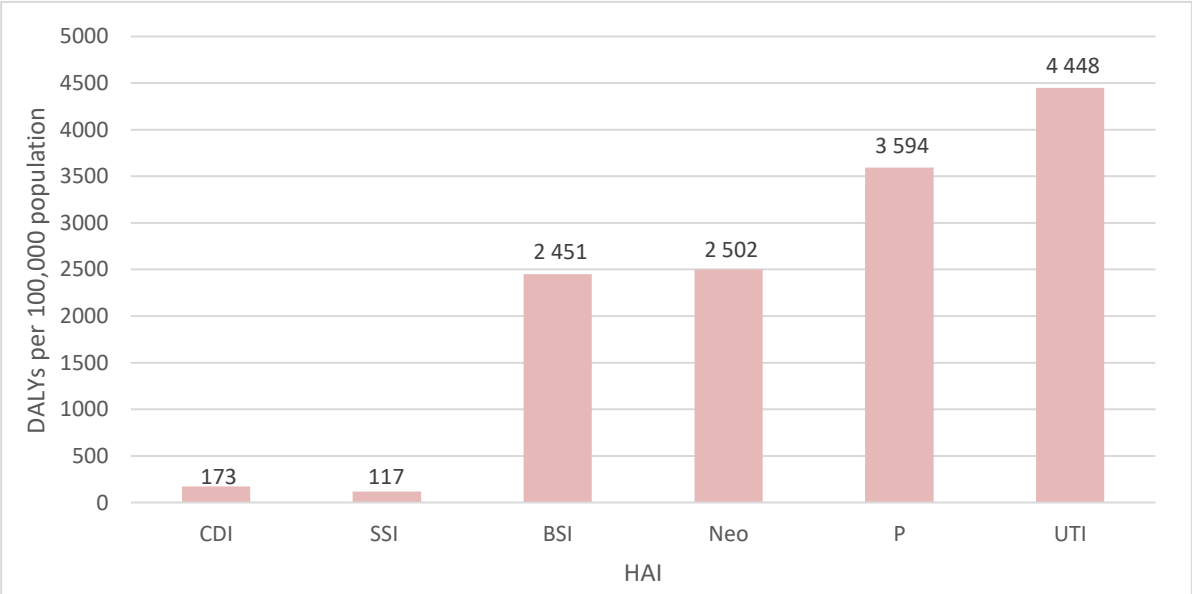

Figure 2.5 - Number of DALYs of incidence of the six healthcare-associated infections (HAIs) per 100,000 inhabitants, Mainland Portugal, 2016

HAIs accounted for 13,225 DALYs per 100,000 general population. As shown in Fig. 2.5, The HAI with more DALYs per 100,000 general population is UTI with 4,448 per 100,000. CDI and SSI are the infections with the lowest number of DALYs per 100,000 general population with 173 per 100,000 and 117 per 100,000, respectively.

Discussion

Using the mentioned scientific approach, the burden of HAI expressed in DALYs for the whole Mainland Portugal was estimated which provides the possibility to identify public health threats and ways to improve health based on evidence [61] and a possible answer to essential goals of WHO defined by the AMR and HAIs Health Burden Estimation working group [62].

For our best knowledge, this is the first study in Portugal which addresses the topic using the country as a whole, and that led to refer that all age groups are affected by the HAIs, and their burden is significantly higher in children until 17 years old, 34.84% (considering Neo). Without considering Neo the burden in this age group reduces substantially to 15.92% and the new age group with higher burden is the one with elderly between 65 and 79 years. The age group with the lowest burden of disease is the one that includes adults between 80 and 108 years old (12.24%). Being this the first national study, it becomes more difficult to compare the observed results by age group with other national statistics or results.

Contrarily to Cassini et al.'s study [1] where Pneumonia is the HAI with the highest-burden (33.70%) and the first in rank of DALYs per 100,000 population, in this study the HAI with the highest burden of disease was the UTI (33.64%) and only in the second place, Pneumonia represented 26.72% of the total burden of HAIs under study and is the second in raking of DALYS per 100,000 population. Despite the disagreement with Cassini et al.'s results, the estimated burden of UTIs for Portugal agrees with Otter's publication about HAIs and its burden [6] which puts the UTI on the top of the HAIs which causes more DALYs in the real world.

Considering that DALYs promotes the idea of priority in public health [61], it is very interesting to refer that most of the results of this study follow Otter's range of importance for HAIs in the real world [6].

In this study, the number of DALYs per admission with infection is higher than the one obtained by Cassini et al.'s study for all EU/EEA countries, because as ECDC evidenced, [5,56], [63] Portugal presents one of the highest rates of HAIs and given that for Cassini et al. study [1] data of all EU was estimated, this increment would be expectable for Portugal (the global tax in Europe in 2016/2017 was 6.50%, in Portugal was 9.10% and in 2011/2012 in Europe was 5.70% and in Portugal 10.80%).

Surgical site hospital-acquired infections (SSI) have the lowest number of DALYS mainly due to the fact that the majority of SSI infections when they occur do not imply an admission in the hospital and based on that only severe SSI would have be registered in the database used in the study. Besides this limitation, the result of a low weight of YLD (1.36%) and a high weight of YLL (98.64%) for SSIs is coincident with Cassini et al. study [1].

Bloodstream infections (BSI) have the highest number of DALYs per admission unlike what happens per 100,000 inhabitants, because the quotient between the total number of BSI DALYs and the number of admissions is not proportional to the quotient of the total number of BSI DALYs and the number of inhabitants. This means that the number of inhabitants is higher than the number of BSI admissions and leads to different results.

Comparing with Cassini et al. [1], the number of total DALYs is 116,907 for the 883,952 people considered in this study of Mainland Portugal (13,225 DALYs per 100,000 population), and is much more significant than the EU/EEA in the same year (501 DALYs per 100,000 general population). This fact can occur by three motives: first, the limitation of not having the number of HAIs directly; second, the infection rate in Portugal is higher than that of EU/EEA; third, this study uses the total Portuguese population, while in Cassini et al. a sample of the hospitals patients in EU/EEA was used (in some more prominent countries only few hospitals were counted [56],[63].

Considering the number of admissions with registered infection, this number can be underrated because of the methodology used to report the codification of the infections and, consequently, it depends on the codifier and the hospital.

There are other limitations that need to be addressed: the outcome trees used were built on available published evidence, and the resulting disease progression pathway may not always entirely reflect the definition of a case of HAI, but they were the best available approximation, as Cassini et al. [1] explained and only six types of HAIs were studied and may lead to an underestimation of the total burden of HAIs in Portugal.

Besides these limitations, this is an innovative study using for the first time data at national level which estimates the healthcare-associated infections DALYs and provides ways to address this public health challenge and implement directional strategies which can be more productive and reduce the future cost of HAIs in Portugal.

For future work, taking into account the Friedrich study [64], DALYs will be calculated at regional level because regional and local dynamics can influence some results in public health, specially the HAIs ones and also a suggestion to *Administração Central do Sistema de Saúde*, IP will be sent to include a variable on the National Morbidity Database that accounts for HAIs or non-HAIs for each infection diagnosis.

Conclusions

This is the first study that estimates the burden of disease for HAIs in Mainland Portugal at national level. Using DALY it was possible to estimate that during 2016 there were 11,467 cases of HAIs in Mainland Portugal which caused 116,907 disability-adjusted life years.

BSI, Pneumonia and UTI were three of the HAIs with higher burden of disease (apart from Neo) which corresponded to 13.43, 10.95 and 10.69 DALYs per admission with infection. These alarming results show that it is necessary to take a path of efforts to reinforce the health politics in this area.

The results of this work are mostly aligned with other studies' results, adjusted by the reality in Portugal, a country with one of the highest infection rates in the EU/EEA area.

Chapter 3: Tastings and flavours about costs of Healthcare-Associated Infections in Portugal: an insight using administrative hospital data

In this chapter, the costs of the healthcare-associated infections in Mainland Portugal and their impact on the Portuguese National Health System (SNS, *Sistema Nacional de Saúde*) will be analysed.

The Diagnostic Related Groups (DRG) constitute a classification system of inpatients in hospitals that group the patients in clinically coherent and similar groups from the point of view of the consumption of resources. It operationally defines the products of an hospital, set of goods and services that each patient receives according to his needs and pathology that leads him to the hospitalization and part of the defined treatment process [65].

Length of stay (LOS) is the used total number of days by each inpatient in the multiple services of a health establishment in a reference period, except the discharge day from that health establishment [66].

The DRG price involves all provided services during the hospitalisation, whether in the hospital ward or in intensive care units, including all medical care, complementary diagnostic and therapeutic means, as well as hospitality [66].

For each episode there can only correspond one DRG, from the admission date until the discharge date, regardless of the number of services in which the patient has been treated [66].

The episodes of admission classified in DRG can be normal/typical or exceptional (short duration or prolonged evolution) in function of the time variable of LOS. Normal or typical episodes present longer LOS than the inferior threshold (minimum number of days in the estimated range of length of stay considered by Portuguese Hospital Morbidity Database) and shorter LOS than the superior threshold (maximum number of days in the estimated range of length of stay considered by Portuguese Hospital Morbidity Database). Short duration episodes present the admission time equal or inferior to the inferior threshold of DRG in what they were classified. Prolonged evolution episodes show admission time equal or superior to the high threshold of the DRG respective. Typical/normal and prolonged evolution episodes correspond to 1 equivalent patient (Eqv.). Short duration episodes correspond to less than 1 equivalent patient, $Eqv = \frac{Length\ of\ stay}{Lower\ threshold}$ [66].

Inpatients with less than a 24-hour stay, who get out of the hospital against doctor orders or who die are considered as short duration patients. Inpatients with less than a 24 hours, transferred to another health establishment are not considered as equivalent patients [66].

If a patient stays in the health establishment less than 24 hours, even if he stays during the night, his/her episode is paid as an ambulatory episode (medical or surgical). The concept of DGR of ambulatory applies only to the programmed admissions, whether in surgical activity or in medical activity. Ambulatory surgery is a programmed surgery that is realised as an outpatient care service with a recovery period less than 24 hours even though it is effectuated in an inpatient facility effectuated in hospitalisation regime. The base price for programmed admissions, medical and surgical ambulatory is 2,285€ [66].

In this exploratory work the LOS was not considered in the costs, because in spite of it is needed for the calculations of the equivalent patients, these values were already presented in the Portuguese Hospital Morbidity Database [66].

3.1 Working Paper II, submitted to "Acta Médica Portuguesa"

Tastings and flavours about costs of Healthcare-Associated Infections in Portugal: an insight using administrative hospital data

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Summary

Objectives This study aims to fill the that exists in Portuguese literature on healthcare-associated infections (HAIs) costs and to alert healthcare system responsible of excessive costs.

Methods The relevant cases for this study were estimated using the National Hospital Morbidity Database which contains the admissions records for 2016 corrected by the data from the European Centre for Disease Prevention and Control (ECDC) Point Prevalence Study. To calculate the inpatient cost the rule defined for 2016 ACSS's circular invoice was considered and then it was divided by the number of infections to determine the adjusted cost. To estimate the average cost for HAI per 100 admissions and per age group averages based on the weight of APR31 severity levels that are mentioned on the ACSS database were calculated.

Findings In 2016, 11,467 cases of HAIs were estimated. Urinary tract infection (UTI) was the HAI with the highest number of infections, 32.09%. This HAI is also the most expensive in Mainland Portugal corresponding to 10.93€ million, while *clostridium difficile* (CDI) is the cheapest, 0.79€ million. Considering the average cost by admission with HAI, neonatal sepsis costs 4,091.69€ being the most expensive.

Conclusions This is the first study that uses national data to estimate the costs of HAIs in Portugal. UTI was the most expensive HAI and Neo had the major costs per admission. Bloodstream infection (BSI) had the lowest cost per admission due to individuals that die before they reach the minimum expected number of inpatient or the individuals can have other infections affecting the average costs calculations. The average costs in Portugal are different than other countries, because the prevalence of HAIs in Portugal is higher than those countries. The total costs of this HAIs round the 33€ million and their reduce need to be a priority for the portuguese healthcare responsible.

Introduction

Healthcare-associated infections (HAIs) are related with increased morbidity and mortality and excess costs, and because a significant proportion of them are preventable, they are considered to be a marker of quality of patient care [67].

Considering the existence of interventions described in the literature that can substantially reduce the incidence of HAIs, [68] and of analyses indicating that at least 50% of them are preventable [69,70], it urges to study why, e.g., in the USA, roughly 1.7 million hospital-associated infections occur annually in acute-care hospitals [4] and why HAI costs approximately 7€ billion in Europe [3].

In Portugal, studies that estimates extra costs of around 10,000€ per patient with one central line-associated bloodstream infection (CLABSI) [71] and a total cost of 407,999,814€ for five HAIs in *Centro Hospitalar Universitário de Lisboa Central* (CHULC) [72] were published. Associating these results with those of the European Centre for Disease Prevention and Control (ECDC) of 2012 and 2017, where Portugal is very bad positioned [5,63], the need of more studies in this area is enhanced.

Despite an public health mandate to minimize the occurrence and impact of HAIs, identifying the most cost-effective or even effective strategies to do so is a source of uncertainty [73]. A number of strategies have been proposed, ranging from environmental controls and modifications to the education of patients and health care providers on hand hygiene [73]. Invariably, hand hygiene is a part of any effort to control HAIs [73], however, despite the availability of solutions, the strong ethical case for improvement, and the intuitive argument that saving lives ought to save money, large-scale progress against HAIs has been slow. Only recently have health care organizations begun to achieve successes and overcome doubts about the scalability of pilot studies [74].

It is well known that elderly people are more vulnerable for the acquisition of infections than younger population and have higher mortality and morbidity rates due to infections [75]. According to some studies [75–77], elderly individuals are at higher risk of developing HAIs, possibly in part of the immunosenescence, [75] and have statistical higher mortality rates than the rest of the patients (with HAIs) [78,79]. Besides this, mortality rates are higher in patients that developed HAIs than patients who did not, both in elderly and non-elderly groups [80,81].

The inappropriate use of antibiotics contributes to antimicrobial-resistant bacteria in hospitals and in the community [2,82]. Dealing with Antimicrobial Resistance (AMR) complications could cost up to USD 3.5 billion a year on average across the 33 countries included in the OECD analysis [82]. Between 2015-2050, Italy, Greece and Portugal are forecasted to top the list of OECD countries with the highest mortality rates from AMR [82].

Besides the AMR/HAIs problem in Portugal, there is a lack of Portuguese literature on the issue of HAIs costs, where only local studies were possible to find [71,72].

This study aims to fill this gap, by being the first at national level which estimates the costs associated with the most significant and targetable HAIs in the country. By attesting the existence and magnitude of such consequences, an important step is taken in order to help the definition and adoption of the best prevention campaigns and/or alternative payment systems [72].

Methods

To ensure that the previous objectives are achieved, a study was designed based on Chapter 2, using the same data but with the goal to study the costs of those inpatient records.

The HAIs considered in this study are the following: urinary tract infection (UTI), primary bloodstream infection (BSI), neonatal sepsis (Neo), *Clostridium difficile* infection (CDI), surgical site infection (SSI), and pneumonia (P).

For this study data from the National Hospital Morbidity Database provided by *the Administração Central do Sistema de Saúde, IP* (ACSS) was used, regarding the inpatient records of 2016 in Mainland Portugal.

During 2016, 1,632,375 inpatient records were observed. Using Chapter's 2 methodology only 159,304 cases with at least one diagnosis of infection were selected, which included cases of HAIs and non-HAIs.

To estimate the cost of each admission the rule defined for 2016 ACSS's circular invoice [66] was considered, which calculate the cost of an inpatient record i, i=1,…,159,304, as the result of the following formula:

$$Cost\ of\ admission_i = 2{,}285 \times RW_i \times Eqv_i$$

where 2,285€ is the Portuguese standard price for all Diagnostic Related Groups (DRG), RW_i is the relative weight for DRG_i and Eqv_i corresponds to the number of equivalent patients relative to the DRG_i.

RW represents the quantity of resources that was used for each admission, where the standard weight is 1 and is comprehended in [0, +∞ [. Regarding the number of equivalent patients it is [66].:

$$Eqv_i = \begin{cases} \frac{LOS_i}{LL_{DRG_i}} \ (<1), if & LOS_i < LL_{DRG_i} \\ 1, if & LL_{DRG_i} < LOS_i < UL_{DRG_i} \\ 1, if & LOS_i > UL_{DRG_i} \end{cases}$$

Where, LL_{DRG_i} is lower length and UL_{DRG_i} is upper length.

Taking into account that there is the possibility to have in one admission i more than one infection, the calculated cost was adjusted by the number of infections of the admission:

$$Adjusted\ Cost_i = \frac{Cost\ of\ admission_i}{Nº\ of\ infections_i}$$

where the cost of admission and the number of infections corresponds to the admission i=1,…,159,304.

Due to the fact that the scope of the paper is only related with HAIs, the number of cases included dropped to 11,467 after correction for the incidence of each HAI [56]:

$$Adjusted\ Cost_{i,j} = \frac{Cost\ of\ admission_i}{Nº\ of\ infections_i} \times Weight\ of\ HAI_{\ i,j}$$

where the cost of admission and the number of infections is related with admission i=1,…,11,467 and $weight\ of\ HAI_{i,j}$ corresponds to the percentage of $HAI_{\ j}$ in the admission i of a patient with an infection j=1,…,6.

$$Weight\ HAI_{i,j} = \begin{cases} weight\ of\ HAI_j, if\ patient\ i\ has\ HAI_j \\ 0, \qquad otherwise \end{cases} \qquad HAI_j = \begin{cases} 1, \ if\ HAI = CDI \\ 2, \ if\ HAI = SSI \\ 3, \ if\ HAI = BSI \\ 4, \ if\ HAI = Neo \\ 5, \ if\ HAI = \ P \\ 6, \ if\ HAI = UTI \end{cases}$$

To estimate the average cost for HAI per admission averages based on the weight of APR31 (All Patient Refined, DRG version 31) severity levels that are mentioned on the ACSS database were calculated.

For the average cost adjusted by HAI we have:

$$Average\ adjusted\ cost_i = \frac{\sum_j Adjusted\ Cost_{i,j}}{No\ of\ HAI_i} \quad (3.1)$$

where the costs and admissions is related with infection i=1,…,11,467.

The result of (3.1) was corrected taking into account the weight of the HAIs in the total infections, according to Chapter 2.

To use and extract data from the National Database of Hospital Morbidity in this study the computer program IBM SPSS Statistics 25 was used.

Results

The distribution of cases by HAI and by age group is represented in Fig. 3.1, where Pneumonia (P) and Urinary Tract Infections (UTI) are the infections with the most cases, 24.87% and 32.09%, respectively. *Clostridium difficile* infection (CDI) is the one with less cases (2.80%), not considering sepsis neonatal (Neo) because it only affects children with less than 1 year old. The age group of [80,108] is the one that has the higher incidence (not considering Neo) with 40.19% of the total infections.

Analysing the most incident infection per age group, for [0,17] years the most incident infection is Neo with a weight of 31.05 %. In the age's group [18,49] and [50,64] years groups the HAI with more weight is SSI with incidences of 46.58% and 40.30%, respectively. Between [65,79] and [80,108] years, UTI is the HAI with more cases, 31.60% and 39.15%, respectively.

The number of admissions increases in all age groups, especially from [50,64] to [65,79] and then, again, from [65,79] to [80,108]. The number of infections between 18 and 49 years old represents 8.50% of the total admissions in that group age and the number of infections in the age group of [80,108] only represents 6.48% of the admissions, the lowest percentage.

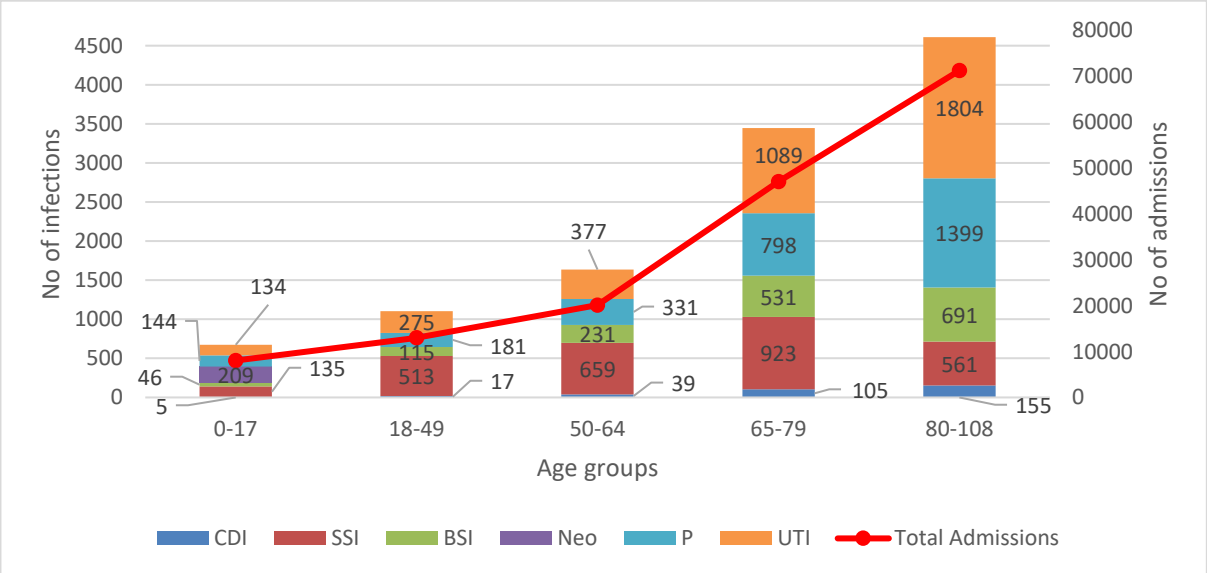

Figure 3.1- Number of cases by age group of the six healthcare-associated infections (HAIs) considering the total admissions by HAI, Mainland Portugal, 2016

Regarding the total adjusted cost in function of age group by HAI, the age group of [80,108] is the most expensive, 12,109,066.94€ (36.68%). The age group of [0,17] is the one with less costs (7.12%).

Fig. 3.2 presents the total adjusted cost by HAI, where UTI is the most expansive infection (10.93€ million), while CDI is the cheapest (0.79€ million).

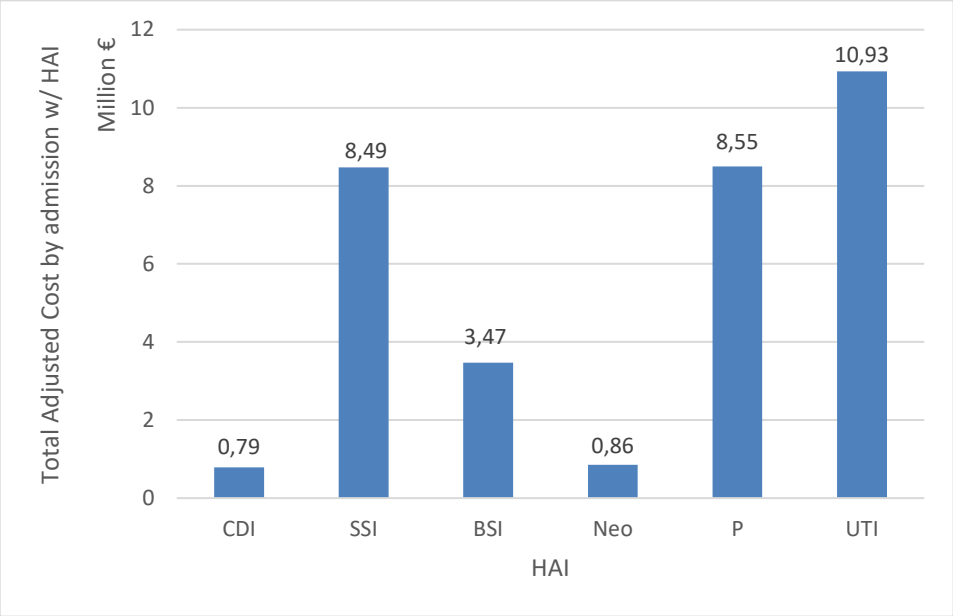

Figure 3.2- Total adjusted cost by admission with HAI, Mainland Portugal, 2016

Fig. 3.3 shows the total average adjusted cost by admission, where Neo is the most expensive, 4091.69€, while BSI is the cheapest, 2151.31€.

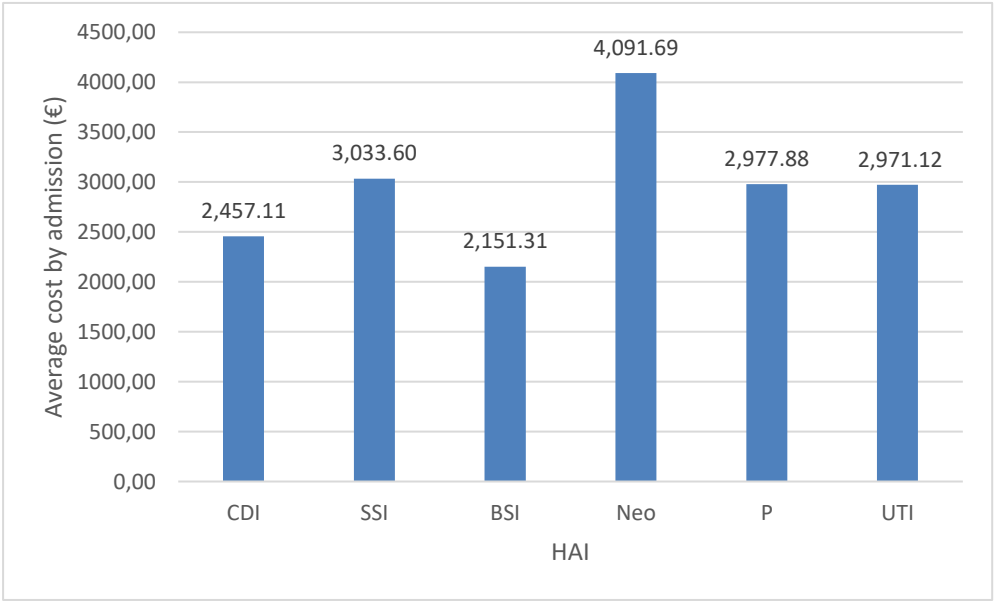

Figure 3.3- Average adjusted cost by admission with HAI, Mainland Portugal, 2016

Discussion

In Portugal, in 2016, the six HAIs in study had a total estimated cost of 33,010,424.88€. CDI was the cheapest HAI with a cost of 788,733.01€, and UTI the most expensive one, corresponding to 10,933,738.33€. The age group of [0,17] had lowest costs (7.12%) and the age group of [80,108] had the highest costs (36.68%). Considering the average cost by admission with HAI, BSI had the lowest cost of 2,151.31€ and Neo the highest, 4,091.69€.

The fact that bloodstream infection is the HAI with the lowest total average adjusted cost per admission (2,151.31€) can occur due to two reasons. This serious infection can have a very high number of deaths [83–86] and, consequently, the individuals die before they reach the minimum expected number of inpatient (3.55%), or the individuals with BSI can also have other infections (70.23%) and in the calculations of the average cost, this cost was divided by the number of infections and, possibly, turned out a lower value than expected.

On the other hand, Neo is a HAI with one of the lowest total cost, but according to Fig. 3.3 it is the most expensive per admission with HAI. This can be explained by the lower number of admissions with this HAI (209 admissions), the high severity of the HAI and, consequently, consuming more resources [87].

The average cost of UTI in Portugal was 2,971.12€, a way more than in the USA, $896 to $1006 (≈802.17€ to 900.65€) [88]. The average cost of CDI by admission is 2,457.11€ a way less than the cost by case in the USA of $11,285 (≈10,103.18€) [74]. For BSI the average cost by admission is 2,151.31€, which is low cost comparing to the USA average cost, $1,822 to $110,800 (≈1631.19€ to 99,196.47€) [88]. In this study, SSI has an average cost by admission of 3,033.60€ and in the USA these infections are responsible for a cost of $20,875 (≈18,688.87€) per admission [74].

This difference between the costs of the HAIs in Portugal and in other countries, like United States, comes from the fact that the incidence of HAIs in Portugal is lower than in the other countries [74]. It can exist an underrated incidence in Portugal, because diagnostic data was used and no data was collected especially for this study.

This study has some limitations to consider, like the fact that the data relative to the costs of the infections in study covers the HAIs and non-HAIs, where there is no discrimination between the two groups and we needed to using the number of HAIs of Chapter 2. This leads to consider the same costs for HAIs and non-HAIs [89].

Other important concepts to ponder when determining the attributable costs of HAIs are comorbidity conditions, as well as length of stay (LOS) in the hospital prior to acquiring the infection [90]. Considering this as the first national study about HAIs' costs using the comorbidities and LOS would leave no room for other publications in the field, which seem to be of extreme importance. So, those will be considered in future papers. Nonetheless, it is recognised that without an adjustment for comorbidities or LOS can result in more expensive HAIs [91].

Other interesting aspect to contemplate and, also a future line of investigation, is the fact that the problem of HAIs is related with the problem of AMR. With an increase in the prevalence of resistant organisms and incentives to discharge patients quickly while minimizing readmission rates, concerns about HAIs will likely be higher [73].

Conclusions

This study will help reinforce the literature about the costs of HAIs in Portugal, in other to give more clarification to the community, specially to the scientific community. This study is also an innovator one, because is the first to use national data of all the public hospitals in Portugal Mainland to estimate the costs of HAIs.

UTI is the most expensive HAI in Portugal Mainland (considering the total costs), 10.93€ million and CDI is the cheapest, 0.79€ million, but per admission Neo is the most expensive, costing 4091.69€ to Portuguese national healthcare system (SNS, *Sistema Nacional de Saúde*). BSI only costs 2,151.31€ due to individuals that die before they reach the minimum expected number of inpatient or the individuals can have other infections affecting the average costs calculations.

The results of this study are estimated costs and must be careful analysed, because this work is of explorative nature, nonetheless representing a country. These costs are a starting point for further analyses but can nonetheless give an alert of excessive costs to the healthcare system responsible.

Chapter 4: Conclusion

The aim of the present study was to estimate the national healthcare burden associated with HAIs, in Mainland Portugal, during a 1-year time horizon.

Through this work it is possible to characterize the burden of disease of the most frequent six HAIs, in Portugal Mainland, in 2016. It was concluded that occur 11,467 cases of these six HAIs with a correspondent 116,907 DALYs. UTI was the most incident HAI corresponding to 39,322 DALYs with an average age of 72.92 years and SSI was the HAI with less incidence, 1,033 DALYs, and 61.77 years old of average age. BSI was the HAI with the higher burden, 13.43 DALYs per admission with infection. SSI is again, the HAI with less DALYs per admission with infection, 0.37 DALYs.

Analysing the costs of the HAIs (33,010,424.88€), the age group of [0-17] was the cheapest (7.12% of the total costs) and the age group of [80-108] the most expensive (36.68% of the costs). UTI was the HAI with major total costs, 10.93€ million and Neo was the most expensive HAI per admission with infection, 4091.69€. Portugal had a higher incidence of HAIs than other countries and because of this it had higher costs than these countries.

Results are significant and in line with literature, adjusted by the reality in Portugal, a country with one of the highest infection rates in the EU/EEA area.

The present study has quantified the substantial socio-economic burden that HAIs place on the healthcare system in Portugal to be of 116,907 DALYs and 33,010,424,88€ per year. These results are alarming and show that is necessary to undertake efforts to reinforce health politics in this area. However, our analysis was conservative and the total burden is expected to be greater, both clinically and economically. This study is the first at a national level presenting the results about six of the most common HAIs from the point of view of DALYs and costs, but can also be starting point for further analyses. Nonetheless it gives an alert for the excessive expense with HAIs, making its reduction a priority.

DALYs have also some limitations. Being a measure of mortality and health status, this measure cannot include considerations of pain and discomfort, nor of the broader demands of caring and nursing which accompany some conditions of ill-health. It is also an effectiveness measure, depending on assessing outcome, not considering the situation of deprivation. The discounting life is also a problem, according to the philosophic optic, especially for people with life-long disabilities because their lives should be valued equally to those of people with no disabilities. It is considered a form of discrimination against people with disabilities [92]. But despite of these critics, DALYs give very good information about health state of the patients, informing when to act and where the resources needed to be relocated. It is a very good indicator for the burden of disease. DALYs can be complemented with patient-reported outcome measures (PROM) that are questionnaires completed by patients to measure their perception of their functional well-being and health status, questionnaires EQ-5D and SF-36, for instance [93].

Findings (confirming expectation of high values of DALYs and costs associated to these infections) have important policy implications such as decision of investing in prevention campaigns and other infection control interventions to reduce HAIs incidence. In this model, HAI incidence could be varied to examine the clinical and economic impact of its reduction.

The bespoke health economic model developed for this analysis, based on these data, may be a valuable tool for future clinical and economic evaluations of infection control strategies in Portugal.

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Annex

Annex I

Table A- ICD-9 codes

HAI	ICD-9 code	Code description
C. difficile infection (CDI)	008.45	Intestinal infection due a C. difficile
Urinary tract infection (UTI)	590.1	Acute pyelonephritis
	590.10	Acute pyelonephritis without lesion of renal medullary necrosis
	590.11	Acute pyelonephritis with lesion of renal medullary necrosis
	590.2	Renal and perinephric abscess
	590.3	Pyeloureteritis cystica
	590.8	Other pyelonephritis or pyonephrosis, not specified as acute or chronic
	590.80	Pyelonephritis, unspecified
	590.81	Pyelitis or pyelonephritis in diseases classified elsewhere
	595.0	Acute cystitis
	595.89	Other specified types of cystitis
	595.9	Cystitis, unspecified
	597.80	Urethritis, unspecified
	599.0	Urinary tract infection, unspecified
	771.82	Urinary tract infection of newborn
	996.64	Due to indwelling urinary catheter
Pneumonia (P)	480.0	Pneumonia due to adenovirus
	480.1	Pneumonia due to respiratory syncytial virus
	480.2	Pneumonia due to parainfluenza virus
	480.3	Pneumonia due to SARS- associated virus
	480.8	Pneumonia due to other viruses not elsewhere classified
	480.9	Viral pneumonia unspecified
	481	Pneumococcal pneumonia/ streptococcus pneumoniae pneumonia
	482.0	Pneumonia due to Klebsiella pneumoniae
	482.1	Pneumonia due to Pseudomonas
	482.2	Pneumonia due to Hemophilus influenza; H. influenzae
	482.3	Pneumonia due to streptococcus
	482.30	Pneumonia due to streptococcus; streptococcus unspecified
	482.31	Pneumonia due to streptococcus; group A
	482.32	Pneumonia due to streptococcus; group B
	482.39	Pneumonia due to streptococcus; other streptococcus
	482.4	Pneumonia due to staphylococcus
	482.40	Pneumonia due to staphylococcus, unspecified
	482.41	Methicillin susceptible pneumonia due to staphylococcus

Pneumonia (P)	482.42	Methicillin resistant pneumonia due to staphylococcus
	482.49	Other staphylococcus pneumonia
	482.8	Pneumonia due to other specified bacteria
	482.81	Pneumonia due to other specified bacteria; anaerobes
	482.82	Pneumonia due to other specified bacteria; Escherichia coli
	482.83	Pneumonia due to other specified bacteria; other gram-negative bacteria
	482.84	Pneumonia due to other specified bacteria; legionnaires' disease
	482.89	Pneumonia due to other specified bacteria; other specified bacteria
	482.9	Bacterial pneumonia unspecified
	483.0	Pneumonia due to other specified organism; mycoplasma pneumoniae
	483.1	Pneumonia due to other specified organism; chlamydia
	483.8	Pneumonia due to other specified organism; other specified organism
	484.1	Pneumonia in cytomegalic inclusion disease
	484.3	Pneumonia in whooping cough
	484.5	Pneumonia in anthrax
	484.6	Pneumonia in aspergillosis
	484.7	Pneumonia in other systemic mycoses
	484.8	Pneumonia in other infectious diseases classified elsewhere
	485	Pneumonia, organism unspecified
	486	Bronchopneumonia, organism unspecified
	487.0	Influenza with pneumonia
	997.31	Pneumonia associated to a ventilator
Neonatal sepsis (Neo)	771.81	Sepsis of newborn
Bloodstream infection (BSI)	995.91	Sepsis
	995.92	Severe sepsis
	999.31	Infection due to central venous catheter
	999.32	Bloodstream infection due to central venous catheter
	999.33	Local infection due to central venous catheter
	038.9	Unspecified septicemia
Surgical side infection (SSI)	324.1	Intraspinal abscess
	478.24	Retropharyngeal abscess (after cervical surgery)
	513.1	Abscess od mediastinum
	519.2	Mediastinitis
	567.2	Other suppurative peritonitis
	567.21	Peritonitis (acute) generalized
	567.22	Peritonietal abscess
	567.29	Other suppurative peritonitis
	567.38	Other retroperitoneal abscess
	567.39	Other retroperitoneal infections
	567.81	Choleperitonitis
	567.89	Other specified peritonitis
	567.9	Unspecified peritonitis
	569.61	Colostomy infection

Surgical side infection (SSI)	614.3	Acute parametritis and pelvic cellulitis
	674.30	Other complications of obstetrical surgical wounds
	674.32	Other complications of obstetrical surgical wounds, delivered, with mention of postpartum complication
	674.34	Other complications of obstetrical surgical wounds, postpartum condition or complication
	682.1	Neck cellulitis and abscess, other
	682.2	Trunk cellulitis and abscess, other
	682.6	Cellulitis and abscess of leg except foot
	686.00	Pyoderma, unspecified
	686.09	Other pyoderma
	686.1	Pyogenic granuloma of skin and subcutaneous tissue
	686.8	Other specified local infections of skin and subcutaneous tissue
	686.9	Unspecified local infection of skin and subcutaneous tissue
	711.06	Pyogenic arthritis, lower leg
	711.66	Arthropathy associated with mycoses, lower leg
	711.96	Unspecified infective arthritis, lower leg
	730.06	Acute osteomyelitis, lower leg
	730.08	Acute osteomyelitis, other specified sites
	730.26	Unspecified osteomyelitis, lower leg
	730.28	Osteomyelitis with or without mention of periostitis, other specified sites
	730.96	Unspecified infection of bone, lower leg
	875.1	Open wound of chest (wall)
	996.60	Reaction-unspecified device/graft
	996.61	Due to cardiac device, implant and graft
	996.62	Due to vascular device, implant and graft
	996.63	Due to nervous system device, implant and graft
	996.67	Due to other internal orthopedic device, implant and graft
	996.69	Due to other internal prosthetic device, implant, and graft
	997.09	Surgical complication nervous system NEC
	998.31	Disruption-internal operative wound
	998.32	Disruption-external operative wound
	998.51	Infected postoperative seroma
	998.59	Other postoperative infection (abscess)

Annex II

Ciências ULisboa

Acesso à Base de Dados de Morbilidade Hospitalar

Aluno (se aplicável): Pedro Miguel Rosa Fernandes

Orientador/Investigador: MARIA ISABEL CARLISTO FRADE BARRÃO

Tipo de documento (se aluno)

- ☒ Dissertação de Mestrado
- ○ Tese de Doutoramento

Entidade(s)

- ☐ CEAUL
- ☐ CMAFcIO
- ☒ DEIO

Login de Ciências: fc46673@alunos.fc.ul.pt

Data de validade da autorização:

Declaro ter conhecimento e respeitar as condições de acesso à Base de Dados de Morbilidade Hospitalar (BDMH), disponibilizada no âmbito de protocolo firmado entre a Faculdade de Ciências da Universidade de Lisboa e a Administração Central do Sistema de Saúde (ACSS), comprometendo-me a:

- Utilizar os dados exclusivamente no âmbito de investigação académica;
- Não disponibilizar os dados a terceiros nem os comercializar de qualquer forma;
- Não realizar cruzamento dos dados com outras bases de dados, nomeadamente na tentativa de violar a anonimização a que os dados da BDMH foram sujeitos;
- Não identificar os nomes dos hospitais constantes da BDMH em material publicável sem autorização expressa do mesmo;
- Não comercializar os dados da BDMH ou os resultados derivados do tratamento aos hospitais que contribuiram com a informação constante da BDMH;
- Por forma a que Ciências cumpra a sua obrigação de comunicação à ACSS, entregar cópia de:
  - todas as utilizações e divulgações que venham a ser realizadas de dados derivados dos disponibilizados na BDMH;
  - todos os relatórios e publicações onde constem dados extraídos diretamente ou derivados da BDHM;
- Reconhecer a colaboração da ACSS em todos os trabalhos resultantes da utilização da BDMH;
- Garantir o tratamento leal e seguro dos dados. Para tal:[1]
  - Aceder preferencialmente aos dados disponibilizados utilizando o serviço de partilha de ficheiros de Ciências, evitando a criação de cópias locais nos computadores de trabalho;[2]
  - Nos casos devidamente justificados em que é criada uma cópia local, manter os dados cifrados[3] eliminando-as logo que cesse a razão da sua criação;
  - Não manter cópias locais após a data de expiração da autorização indicada acima;

Aluno: Pedro Fernandes

Orientadora: Maria Isabel Carlisto Frade Barrão

(Documento assinado digitalmente pelo aluno e orientador (se aplicável) ou investigador)

1 A Direção de Serviços Informáticos está disponivel para apoiar a configuração dos computadores pessoais com as medidas a seguir indicadas presencialmente ou através do endereço de correio eletrónico suporte@ciencias.ulisboa.pt.

2 O acesso ao serviço de partilha poderá ser feita utilizando um browser em https://cirrus.ciencias.ulisboa.pt ou criando uma drive externa indicando o seguinte caminho: davs://cirrus.ciencias.ulisboa.pt/owncloud/remote.php/webdav

3 Recomenda-se a utilização de partições cifradas ou da colocação dos dados em ficheiros compactados (zip) protegidos com password